"FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF SALBUTAMOL SULPHATE USING VARIOUS SUPERDISINTEGRANTS"

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I recommend this research work for acceptance as project for the partial fulfillment of the degree of "**Master of Pharmacy"** of the Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirapalli, for the year March 2008.

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CONTENTS

1. Introduction

1.1 Mouth dissolving Drug Delivery System

The concept of Mouth dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non - compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by paediatric and geriatric patients. Such problems can be resolved by means of Mouth Dissolving Tablet. When put on tongue, this tablet integrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In many cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

The advantages of Mouth Dissolving dosage forms are increasingly being recognized in both, industry and academia. Their growing importance was underlined secularly when European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet that to be placed in the mouth where it disperses rapidly before flowing.

1.2 Desired Criteria for Mouth Dissolving drug Delivery System (MDDS) [1, 2, 3]

Mouth dissolving tablet should – not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.

- Be compatible with taste masking.
- Be portable without fragility concern. Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and Temperature.
- Allow the manufacture of tablet using conventional processing and Packaging equipment at low cost.

Salient Features of Mouth Dissolving Drug Delivery System [2, 4, 6]

- Ease of administration to patients who refuse to swallow a tablet, such as paediatric and geriatric patients and , psychiatric patients.

- Convenience of administration and as accurate dosing as compared to Liquids.

- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of MDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients.

- Rapid dissolution of drug and absorption, which may produce rapid onset of action.

- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, such cases bioavailability of drugs is increased.

- Ability to provide advantages of liquid medication in the form of solid preparation.

- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

1.3 Techniques for Preparing Mouth Dissolving Tablets

Table No.1

TECHNOLOGY	BASIS FOR TECHNOLOGY	COMPANY
Zydis	Lyophilization	R.P. Scherer, Inc.
Quicksolv	Lyophilization	Janssen
Lyoc	Lyophilization	Farmalyoc
Flashtab	Molding	Ethypharm
Orasolv	Molding	Cima Labs, Inc.
Durasolv	Molding	Cima Labs, Inc.
WOWTAB	Molding	Yamanouchi
Fast Melt	Molding	Elan Corpl
Ziplets	Molding	Eurand
Flash dose	Cottan candy process	Fuisz tech ltd
Oraquick	Direct compression	A pharmaceutical
Pharmaburst	Direct compression	Spipharma
Advatab	Direct compression	Eurand
Frosta	Direct compression	Akinainc

Freeze Drying[1, 4]

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation. However, the use of freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva.

Moulding[1, 3, 4, 5]

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time,

Drug dissolution rate and Mouth feel will depend on the type of dispersion or dissolution.

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general, made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

Moulded tablets usually are prepared from soluble ingredients by compressing a powder mixture previously moistened with solvent (usually water or ethanol) 'into mould plates to form wetted mass,(compression moulding). Recently moulded forms also have been prepared directly from the molten matrix in which the drug 'is dissolved or dispersed (heat moulding) or by evaporating the solvent from the suspension at standard pressure (no-vacuum lyophilization).

T.makino, et. al have also developed as compression-moulded mixtures containing drug and combination of starches and sugars with surfaces that have been wetted with suitable amount of water. The wetted mass is compression moulded and dried. Porous tablets with sufficient mechanical strength have been obtained.

Mouldability is defined as the capacity of the compound to get moulded or compressed WOW(without water) tablet is an intrabuccally dissolving compressed moulding comprising granules made with saccharides having low and high mould ability. Low mould ability means

that the saccharides show reduced compressibility by tableting and rapid dissolution. By contrast high molding, saccharine show excellent compressibility and slow dissolution. Wowtab can accommodate high doses of multiparticulate water soluble or insoluble drug and has adequate hardness.

Sublimation[1-4, 6]

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed by Heinemann and Rose,Inert solid ingredients (e.g. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure.

A method of producing fast dissolving tablet using water as the pore forming material has been described by Makino. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Koizumi have developed a new method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material.

Spray-Drying[1-4]

Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. Spray drying technique has been employed by Allen and Wang to prepare fast dissolving tablets. They developed formulation by using mannitol as bulking agent, hydrolysed and non-hydrolysed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (ex. citric acid) and/or alkali material (ex.$NaHC0_3$) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds.

Mass-Extrusion [1]

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

Direct Compression [1, 3,7,8,9]

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that

usually required. As consequences, products with, optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus. All result from insufficient physical resistance.

Disintegrants have major role in the disintegration and dissolution process of Mouth Dissolving Tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature.

The understanding of disintegrant properties and their effect on formulation has advanced during last few years, particularly regarding so called superdisintegrants. Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrant concentration and above that disintegration time remains approximately constant or even increases.

The simultaneous presence of disintegrant with a high swelling force called disintegrating agent and substances With low swelling force (starch, cellulose and direct compression sugar) define "swelling agent" was

claimed to be a key factor for rapid disintegration of table, which also offers physical-resistance.

Patented Technologies for Mouth Dissolving Tablets

Zydis Technology [10]

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving cancer materials when zydis units are put into the mouth; the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelation, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength.

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure porous units to achieve rapid Disintegration. Various gums are used to prevent sedimentation of dispersed drug ,particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs protect the formulation from moisture in environment.

Durasolv Technology[11]

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters.

Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Orasolv Technology [11]

Orasolv Technology has been developed CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Flash Dose Technology[12]

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of as melt-in – mouth tablets prepared using flash does technology is the first commercial product launched by Biovail Corporation flash does tablets consists of self binding shear form matrices are prepared by flash heat processing.

Wowtab Technology[12]

Wowtab technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharine and granulated with a high mouldability saccharine and compressed into tablet.

Flashtab Technology [13]

Prographarm laboratories has patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the

conventional techniques like coacervation, microencapsulation, and extrucion – spheronisation. All the processing utilized conventional tabletting technology.

1.4 Marketed preparations of Melt – in Mouth Tablets

The Current pharmaceutical market for Mouth Dissolving tablets is on increasing trend. Because of strong patient demand, several products have been commercialized.

Table No. 2

Name of Product	Manufacturer & Country	Remark
Imodium Lingual	R.P. Schere corp. USA	Fast Dissolving Formulation of Imodium
Pepcidin Rapitab	Mktd. By Merck & co., USA	Quick Releasing ant ulcer preparation of pepcid
Mosid – MT	Torrent Pharmaceuticals, India.	Mouth melt tablet of Mosapride citrate.
Calritin Reditabs	Mktd. By Schering Plough Corp., USA	Immediate Dissolving Formulation citrate.
Nimulid – MD	Panacea Biotech, India	Mouth Dissolving tablet of Nimesulide
Zyrof Meltab	Zydus Cadila, India	Melt – In – Mouth tablet of Roefecoxib

Advantages

Ease of administration to paediatric and geriatric patients and psychiatric patients. Bioavailability of drugs is increased No need of water- convenient for travelers Good mouth feel- changes the basis view as " bitter pill". Particularly of peadiatric. Produce rapid onset of action convenience of administration and accurate dosing as compared to liquids. Ability to provide advantages of liquid medication in the form of solid preparation.

1.5 INTRODUCTION TO ASTHMA[14]

Asthama is defined as a chronic inflammatory disorder of the airways in which many cells such as mast cells, eosinophils, T- lymphocytes, macrophages, neutrophils and epithelial cells and cellular elements play a role.

In susceptible individuals recurrent episodes of wheezing, breathlessness, chest tightedness and coughing. These symptoms are usually associated with airflow obstruction. The inflammation causes an increase in bronchial hyper responsiveness (BHR) to a variety of stimuli.

The major characteristic of asthma includes a variable degree of airflow obstruction (related to bronchospasm, edema, and hypersecretion) BHR and air way inflammation.

Up to 150 million people suffer from asthma in the world and the number has been rising steadily. The condition proves fatal for around 1,80,000 of the world's population every year. In India, there are about 20 million asthmatics among which 15 % are children aged between 5 to 11 years, having symptoms.

Asthma attacks caused by both unknown and known factors such as exposure to allergens, viruses, pollutants which may induce anti-inflammatory response.

Inhaled allergens causes an early phase allergic reaction due to activation of cells bearing allergen-specific IgE antibodies. There is a rapid activation of airway mast cells and macrophages, which release anti-inflammatory mediators such as histamine that induces

- Contraction of airway smooth muscle
- Mucus secretion
- Vasodilatation
- Exudation of plasma in the airways

Plasma protein leakage induces a thickened, engorged, edematous air way leading to a narrowing of airway lumen reducing mucus clearance.

The late phase inflammatory reactions occurs 6 to 9 hrs after allergen provocation and involves recruitment and activation of eosinophils, T - lymphocytes, basophils, macrophages and neutrophils.

Mast cells degeneration in response to allergens result in increase of mediators such as histamine, eosinophil and neutrophil chemo tactic factors leukotrienes C4, D4 and E4 induces smooth muscle constriction and bronchospasm results in mucosal edema and mucus secretion.

Alveolar macrophages releases inflammatory mediators including PAF (Platelet Activating Factor) and leukotrienes B4, C4 and D4. They are important pre inflammatory mediators in asthma which are derived from the metabolism of membrane phospholipids within alveolar macrophages,

eosinophils, mast cells and neutrophils. Leukotrienes interact with specific receptors found in various tissues including the lung. Administration of leukotriene solution or aerosol to the airways mimic many of the inflammatory symptoms of asthma including

- Bronchoconstriction
- Increased micro vascular permeability (EDEMA)
- Leukocyte activation
- Eosinophilia
- Enhanced mucus secretion

Leukotrienes are formed when the enzyme 5-lipooxygenase in conjunction with cofactor 5-lipooxygenase activating protein metabolizes Arachidonic acid. I t is further converted to Cysteinyl leukotrienes such as LTC4, LTD4 are highly potent inducers of airway smooth muscle contraction and bronchoconstriction.

DRUG TREATMENT IN ASTHMA[15]

The drug treatment of asthma has remained essentially unchanged over the past three decades in terms of the use of corticosteroid, β2 agonist, and theophylline drugs. Asthma treatment has also been improved by the widespread dissemination and implementation of management guidelines emphasizing the pivotal role of first line preventative, anti-inflammatory therapy.

Summary points[16]

The dose of inhaled steroid should be titrated against asthmatic symptoms, peak flow, and usage of β2 agonist drugs. The safest dose of inhaled steroid is the lowest effective maintenance dose producing optimal long term control and quality of life.

Adding second line anti-inflammatory controller treatment such as a leukotriene antagonist or theophylline may be an alternative to immunotherapy with a high dose of inhaled steroid.

If control is inadequate despite optimized anti-inflammatory treatment, it is better to add regular treatment with a long acting β2 agonist drug than a short acting one.

First principles of treatment

The past decade of research has led to a greater understanding of the pathophysiology of asthma and, in particular, the pivotal role of the underlying inflammatory process. Current asthma management guidelines stress the importance of switching off the inflammatory process at the top of the cascade by giving first line preventive treatment with inhaled corticosteroids, thereby reducing the need to provide symptomatic relief with short acting β2 agonists at the bottom of the cascade. Drugs such as long acting inhaled β2 agonists, theophyllines and anti-leukotrienes may also be used as second line "controller treatment" when given with inhaled corticosteroids to improve symptom control and reduce diurnal variability.

These treatment options should be used conjunction with removal of any potential trigger factors.

Common reasons for poor response to treatment

Poor compliance-for example, as a result of having to take drugs (such as cromoglycate) four times daily, or polypharmacy Poor technique in using an inhaler-for example, difficulty with metered dose inhalers. Presence of trigger factors-for example, allergen, smoking, occupation, oesophageal reflux, rhinitis. Wrong diagnosisfor example, having chronic obstructive pulmonary disease, bronchiectasis or heart failure rather than asthma.

Goals

A number of optimal treatment goals should be set for a given patient within the pharmacoeconomic constraints of the available health service provision.

Goals of treatment

To achieve normal percentage predicted values for forced expiratory volume in one second/peak expiratory flow Reduce diurnal variability of peak expiratory flow and symptoms

- Minimize use of reliever β2 agonist drugs
- Optimize quality of life
- Reduce risk of severe exacerbation of asthma

Corticosteroids

Inhaled corticosteroids are the most potent anti-inflammatory agents for treating asthma and act in a relatively non-specific manner by inhibiting a variety of inflammatory cells, cytokine expression, and transcription factors which are involved in the inflammatory disease process. The delivery directly to the airway of relatively small doses of topically active corticosteroid, along with an extensive degree of hepatic first pass inactivation of the swallowed moiety, results in a high therapeutic index-the ratio of anti-asthmatic efficacy to systemic adverse effects. The inhaled corticosteroid drugs are also the most cost effective form of treatment for. preventing asthma.

Dose response relation exact point depends on disease severity and individual sensitivity. Because respirable lung dose improves greatly with the hydrofluoroalkane formulation of beclomethasone, half the dose of the chlorofluorocarbon formulation can be given, and it to target delivery to the inflamed small airways.

Regimen[17]

The modern management of persistent asthma with inhaledcorticosteroid drugs involves starting treatment with a relatively high dose for four to eight weeks in order to gain rapid optimal control. This is followed by a gradual tapering of the dose to determine the lowest effective maintenance dose for a given person. For people with mild to moderate

asthma, effective control can usually be achieved by a once daily regimen when the patient has been stabilized on maintenance treatment at doses of up to 800/mcg/day of budesonide or beclomethasone. Evidence also suggests that early intervention with inhaled corticosteroid drugs may prevent any long term decline in lung function resulting from bronchial fibrosis caused by untreated chronic inflammation

Available data suggest that the beneficial effects of inhaled corticosteroids on disease control will outweigh any potential systemic bioactivity in terms of long term growth in asthmatic children. No effect of these drugs on the final achieved adult height has been shown. Indeed, other factors such as socioeconomic status and, perhaps, nutrition may be more important in determining height in asthmatic children taking inhaled corticosteroids Corticosteroid induced osteoporosis may be reduced by the use of oestrogen replacement therapy or biphosphonate drugs[18].

Long term treatment with high doses of inhaled corticosteroids is associated with an increased risk of a posterior sub capsular cataracts and, to a lesser degree, with ocular hypertension[19]. Skin bruising, an adverse effect of inhaled corticosteroids, is more prevalent in elderly people and is associated with adrenal suppression[20]. Indeed, skin bruising is visible evidence of increased collagen turnover, and should therefore prompt further screening for other tissue specific adverse effects. It may therefore be prudent to perform a regular annual or biennial check up to look for evidence of systemic bioactivity in the skin, eye, adrenal gland, and bone in adults receiving long term, high dose inhaled corticosteroid treatment (>800µlg daily of beclomethasone or budesonide and >400µlg daily of

fluticasone), and to monitor growth in children (>400µlg daily beclomethasone or budesonide and >200µg daily fluticasone).

Local adverse effects

Local adverse effects such as oral candidiasis may be alleviated by using a large volume spacer to reduce the deposition of drug on the oropharynx. The occurrence of oral candidiasis is related to the dose and to the mucosal exposure time to topical corticosteroid. Thus, a once or twice daily dosing regimen will reduce the likelihood, and this can be reduced further by regular mouth rinsing. Using a spacer device has other advantages-there is increased delivery of respirable particles and the coordination problems associated with using metered dose inhalers are reduced.

Leukotriene antagonists

The cysteinyl leukotrienes are metabolites of arachidonic acid comprising leukotrienes C4, D4, and E4. The cysteinyl leukotrienes cause smooth muscle constriction and proliferation and are important mediators in the pathophysiology of the inflammatory process. The leukotriene antagonists such as zafirlukast (twice daily) and montelukast (once daily) are well tolerated, seem effective over a wide spectrum of disease severity, and exhibit both bronchodilator and antiinflammatory activity[21]. Responsiveness to leukotriene antagonists varies and may be genetically determined by the degree of leukotriene synthesis resulting from 5-lipoxygenase activity. In the United Kingdom, montelukast is licensed in patients aged 6 years and over

as second line asthma controller treatment in combination with inhaled corticosteroids. It is only licensed as monotherapy in the prophylaxis of exercise induced asthma. Zafirlukast, however, is currently licensed in patients aged 12 years and over, including first line use instead of inhaled corticosteroids[22].

Advantages

One of the main advantages of the leukotriene antagonist drugs is that they are active orally, which avoids the potential compliance problems with the inhaled route. The compliance factor with leukotriene antagonists may also be reinforced by the fact that they work within the first 24 hours, while inhaled corticosteroids take much longer to achieve maximal response. The leukotriene antagonists are comparable in cost with long acting β2 agonists, but are much more expensive than low dose inhaled corticosteroids.

Additive effects

Preliminary data with montelukast and zafirlukast suggest that they show additive effects to low or high dose inhaled corticosteroids[22]**.** In multi centre studies, montelukast in children (5mg once daily) or adults (10mg once daily) was better than placebo at controlling asthma over eight to 12 weeks, and this effect was seen equally in patients taking or not taking corticosteroid[25]. In addition, montelukast and placebo showed no differences in adverse effects on biochemical liver function tests. Regular treatment with montelukast produces a sustained, high level of protection against exercise induced bronchoconstriction, in contrast with salmeterol, which

induces tolerance.[26] Another potential advantage of leukotriene antagonist drugs is that they are effective in treating coexistent allergic rhinitis[33], A Churg-Strauss-like syndrome has been reported with zafirlukast and montelukast; this is probably due to an unmasking of the underlying condition caused by tapering of concomitant oral corticosteroids, and reinforces that leukotriene antagonists should not be used instead of oral corticosteroids in dependent patients with severe asthma.

Need for further data

Thus, there seem to be logical reasons for using leukotriene antagonists as second line controller treatment in that they possess both anti–inflammatory and bronchodilator activity, afford bronchoprotection against allergen and exercise, do not exhibit tachyphylaxis, and are well tolerated Bronchial biopsy studies show anti-inflammatory effects of leukotriene antagonists in reducing numbers of T lymphocytes, mast cells, and eosinophils[27]. However, further efficacy and safety data from long term studies are needed to establish the appropriate place of leukotriene antagonists in asthma treatment guidelines-in particular, whether they should be used as an alternative to low dose inhaled corticosteroid as first line monotherapy in patients with mild to moderate persistent asthma

Cromones

The cromones include sodium cromoglycate and sodium nedocromil, which act predominantly by stabilising mast cells. These drugs are well tolerated and have no systemic adverse effects, but they are less effective in treating asthma than inhaled corticosteroids. The cromones tend to be most effective in patients with mild atopic asthma, particularly in children with an exercise or allergen induced component to their condition. However, there is uncertainty about the degree of anti-inflammatory activity of the cromones, at least on the basis of bronchial biopsy studies. Compliance may be a problem with these drugs as they are short acting and need to be taken four times daily. Cromone treatment is also much more expensive than that with low dose inhaled corticosteroid drugs.

Antihistamines

Cetirizine and loratidine are examples of potent, selective, type I histamine receptor antagonists that are well tolerated and are taken on a once daily basis. They have a limited role in treating asthma in patients with a known allergenic trigger factor such as pollen or animal fur. They may also be of value where there is associated seasonal allergic rhinitis and conjunctivitis or if there is associated allergic urticaria. Preliminary data suggest that antihistamines and leukotriene antagonists may show additive effects on control in asthma and allergic rhinitis[25]. Antihistamines should never be used as monotherapy for chronic asthma, but only as an adjunct to inhaled corticosteroids.

Theophyllines

The bronchodilator activity of oral theophylline is relatively weak and high doses are needed. Lower doses of theophylline show anti-inflammatory effects, and this finding led to a reappraisal of theophylline's role as second line controller treatment in addition to inhaled corticosteroids. The advantages of theophylline are that it may be taken once or twice daily as an oral slow release formulation and is inexpensive.

The main disadvantages of theophylline are several important potential drug interactions that may result in drug toxicity as well as the expense and inconvenience of therapeutic drug monitoring. Although the adverse effects of theophylline are related to the plasma concentration, the drug tends to be less well tolerated, even at low doses, than other second line controller drugs such as leukotriene antagonists or long acting β2 agonists

β2 agonists

The β2 agonist drugs act primarily on airway smooth muscle and are the most effective form of bronchodilator treatment. Their effects on smooth muscle and mast cells result in protection against several stimuli of bronchoconstriction. For example, inhaled β2 agonists are highly effective at preventing bronchoconstriction when used shortly before exercise or exposure to known allergens. Evidence suggests that regular use of short acting β2 agonists may worsen control of asthma, although this claim remains contraversies. The requirement for regular use of reliever treatment

with short acting β2 agonists marks an activated inflammatory cascade and hence the need to step up the dose of inhaled corticosteroid

Long acting β2 agonists

The long acting β2 agonists salmetrol and eformoterol became available against this background of recommending short acting β2 agonists for occasional use as a reliever. These drugs are now included in the guidelines for regular. Twice daily use as second line controller treatment in conjunction with a low dose of inhaled corticosteroid. This recommendation is based on studies which showed that adding a long acting ß2 agonist to a low does of inhaled corticosteroid drug produced comparable control to immunotherapy with a higher dose of inhaled corticosteroid.

Concerns

There is concern that the regular use of long acting ß2 agonists may simply palliate the squealae of an activated inflammatory cascade without suppressing the underlying process, particularly as ß2 agonists have no anti-inflammatory activity. None the less, long acting ß2 agonists may be valuable when given regularly for persistent symptoms in patients who would otherwise need to use short acting ß2 agonists frequently, provided adequate anti – inflammatory treatment is also being taken.

We also know that tolerance to the airway effects of ß2 agonists develops when these drugs are regularly and that this is more pronounced for loss of bronchoprotective activity than bronchodilator activity[27,28]. Moreover, the development of tolerance with long acting ß2 agonists occurs in genetically predisposed people. They have a particular variant of the ß2 adrenoceptor, which occurs in up to 50% of white people in the United Kingdom. This genetic polymorphism of the ß2 adrenoceptor may also explain individual variation in the clinical response to long acting ß2 agonist treatment. Eformoterol is a more potent drug and has a faster onset of action than salmeterol. It may therefore be used as required for reliever treatment up to the maximum recommended twice daily dose. This type of "as required" dosing regimen with eformoterol is not recommended in current asthma guidelines. Nor, however, does it seem appropriate to advocate its regular use in every case, particularly if it is not needed all the time. New fixed dose combinations of fluticasone and salmeterol will soon become available in the United Kingdom[26]. Although they might improve compliance, such formulations are less flexible and may inadvertently result in patients taking unnecessary long term treatment with long acting ß2 agonists.

Controlled release oral salbutamol or oral bambuterol (a prodrug of terbutaline) may, like long acting ß2 agonists, be used to treat nocturnal symptoms. Although the oral formulations tend to be associated with systemic effects such as tremor and tachycardia, these usually wear off because of tolerance. None the less, drugs such as bambuterol are less expensive than long acting ß2 agonists and, like theophylline, have the advantage of being taken as a once daily tablet.

Conclusions for drug treatment in Asthma

Inhaled corticosteroids should be used as early as possible as first line anti-inflammatory treatment for patients presenting with symptoms of persistent asthma. For patients who have mild to moderate asthma, there is no proved therapeutic benefit in using more potent and expensive drugs such as fluticasone propionate than older and cheaper drugs such as beclomethasone dipropionate. The therapeutic index for inhaled corticosteroids can be optimised by tapering the dose until the lowest effective maintenance dose is achieved and by using a metered dose inhaler with a spacer device. Second line anti-inflammatory controller treatment may be added as an alternative to monotherapy with a high dose of inhaled corticosteroid in order to avoid any local and systemic adverse effects with the latter treatment. In this respect, there seems to be a rationale for adding treatment with leukotriene antagonists such as montelukast or zafirlukast. These have anti-inflammatory and bronchodilator properties, do not induce tolerance, and can be taken as a once or twice daily tablet. Further long term studies are required to evaluate the position of leukotriene antagonists as first line preventer treatment instead of low dose inhaled corticosteroid drugs in patients with mild to moderate asthma. Theophylline is a cheaper alternative for second line combined anti-inflammatory treatment, but has a lower therapeutic index that requires drug monitoring and shows several important potential drug interactions. If asthma control is inadequate and reliever drugs need to be taken frequently, despite optimized anti-inflammatory treatment, regular treatment with long acting β2 agonists is preferred to that with short acting β2 agonists.

2. Need for the Present Study

Asthma is a chronic Inflammatory disease, which includes bronchial hyper activity and bronchospasm characterized by hyper responsiveness of trachiobroncial smooth muscle to variety of stimuli resulting in narrowing of air tubes, often accompanied by increased secretions and mucosal edema resulting in breathlessness (or) dyspnea wheezing cough, chest congestion and anxiety about being unable to breathe.

Asthma affects over 5-10% of population in industrialized countries. It affects 53 million people across world mostly in United States, France, Germany, Italy, Spain, United Kingdom and Japan. More than 400 people die every year in India as result of complication arising from serials asthma attacks through therefore several recommendations and treatment being reported.

The treatment of asthmatic symptoms generally includes conventional oral dosage like tablets, capsules, oral liquids etc inhalation therapy includes metered oral dose inhalers with (or) without spacers, dry powder inhalers and other aerosol systems an attempt was made for preparation of fast dissolving tablets at model bronchodilator, salbutamal sulphate with an aim of reducing the lag time and providing faster onset of action to relieve immediately acute asthmatic attack..

Disadvantage of other formulation

1. Conventional solid oral dosage forms longer lag time and slower onset of action.
2. Oral liquids provides faster onset of action but require careful handling.
3. Aerosol systems are specific but fail to deliver the actual dose deposited in oropharynz and swallowed.
4. Dry powder inhalers cause clogging of device and require skilful operation.

Advantages of MDDS

A fast dissolving tablet form would thus be advantage as salbutamol is water soluble and preparation into dissolve rapidly and there by result in rapid absorption without any lag time.

3. LITERATURE REVIEW

Yoshiteru.W et.al., [30] Investigated new method of preparing high porosity rapidly saliva soluble compressed tablets of meclizine using mannitol with camphor, a subliming material by direct compression method showed that tablets prepared by this technique have porosity and disintegration time with in 15 seconds in saliva.

Biyx et.al., [31] Carried out formulation studies for ethenzamide rapid disintegrating table containing micro crystalline cellulose, tabellettose and Ac-Di-sol. Tablet was prepared by direct compression technique and Evaluated. Rapid disintegrating tablet with durable structure and desirable taste could be prepared with in the obtained optimum region.

Shirwaikar A.A.et.al., [32] Formulates atenolol fast disintegrating tablet using three superdisintergrants croscarmellose (Ac-di- sol) crospovidone (Polyplasdone) and sodium starch glycoside. Ac- di- sol proved to be best among three and showed satisfactory results.

Yoshutenu .W et .al., [33] Prepared rapid disintegrating tablet in saliva in the mouth by direct compression using micro crystalline cellulose, low, substituted hydroxyl propyl cellulose showed rapid disintegration within 30 seconds was obtained in vitro using compounding ratios at micro crystalline cellulose to low substitute hydroxyl propylcellulose.

Mishra D.N et.al.[37] Formulate Fast dissolving delivery system for valdecoxib". A non- steroidal anti inflammatory drug with valdecoxib and anti inflammatory properties using various super disintegrating agents by direct compression technique and sharing enhanced dissolution.

A Jinichi fukami et. al., [39] Rapidly disintegration table in the oralcavity was prepared using a glycine as a disintegrant. Wetting time prepared from carbox methyl cellulose (Ns – 300) having hardness of 4 kg was 35. Tablet containing (Ns-300) should the fastest disintegration compared to other formulation. it was suggested that the tablet formulation contains Ns- 300 and glycine was highly applicable to water insoluble drug such as ethenzamide.

Masaaki sugimoto et. al., [40] Investigate the effects of crystalline transition of amorphous sucrose in granules on the character of resultant tablets. Prepared by this crystalline transition method. We conclude that rapidly disintegrating oral tablets can effectively be manufactured by the CT method using the granules obtained by fluidized bed granulation method.

Madgulkar A.R et. al., [41] found that ion Exchange resin like Indion 414, and amberliteIRP88 as super disintegrates useful in the preparation of mouth dissolving Delivery system. Indion 414 was found to be better disintegrants.

Bi-y Sunda et.al., [31] He made compressed tablet which can rapidly disintegrate in the oral cavity. Micro crystalline cellulose and low substituted hydroxy propyl cellulose were used as disintegrates. it Shows good correlation between the disintegration behaviors in vitro and in me oral cavity was recognized.

Fausett H, **et. al.,** [34] Develop a rapidly disintegrating calcium carbonate tablet by direct compression and compare it with commercially available calcium tablets. He used cal – carb 4450, cal - carb 4457, and cal – carb 4450, can – carb 4457, and cal – carb 4462 tablets were in the range of 7.2 to 7.7 kg. The D.T was 4.1, 2.1 & 1.9 minutes. This study clearly shows the quick disintegrating cc tablets can be formulated without expensive effervescence technology.

Zhao N, Augusburger LL et. al., [35] To investigate the Influence of swelling capacity of super disintegrates in different pH media on the dissolution of hydro – chlorothizide from directly compressed tablets. The reduced uptake and swelling capacity of disintegrates containing ionisable substituents in acidic medium can potentially jeopardize their efficiency in promoting tablet disintegration and the drug dissolution rate.

Reddy L.H et. al., [36] Frames design for fast dissolving tablets for promethazine theoclate. Tablets were prepared by effervescent melt, superdisintegrant addition and superdisintegrant shows released character was optimal

.

Mishra D.N et. al., [37] Prepared rapidly disintegrating tablets of meloxicam meloxicum is an effective and selective cyclo- oxygenase cox- 2 inhibitor with anti-Inflammatory and analgesic properly tablets were prepared with 3 super disintegrants e.g.: sodium starch glycolate,Ac-Di-Sol and low molecular weight hydroxy propyl methyl cellulose. It was conduced that the rapidly disintegrating tablets proper hardness rapidly disintegrating in the oral cavity with enhanced dissolution can be made using selected super disintergrants.

Shishu et. al., [38] aimed at preparing taste masked granules, rapidly disintegrating tablets of chlorphenmiramine maleate, a bitter drug. The taste masked granules using eudragit E-100 by me extrusion method. Directly compressed into tablets using sodium starch glycolate as a super disintegrants. Successful formulation of oral fast disintegrating tablets which had good taste and disintegrated in the oral cavity with in 30s.

Bi. Y – yonezwa., [33] He made tablets prepared by compressing wet granules under low compression force and they drying the resulting wet mass in a circulating – air oven. Lactose with various particle sizes was used as the excipient. By optimizing compression force, size of the lactose particles, and the moisture content of the granules tablets meeting tensile strength greater that 0.5 mpa and disintegration time shorter than 15 seconds were obtained by the wet compression method

4. AIM AND OBJECTIVE OF WORK

Aim:

The aim of the present was study to formulate the mouth dissolving tablets using super disintegrants and evaluating for its characteristics.

The objective of present study

1. To enhance the solubility of salbutamal sulphate by using superdisintegrants in the oral cavity.
2. To develop mouth dissolving drug delivery system and enhance the patient compliance.

This mouth dissolving tablet of salbutamol will disintegrate rapidly in the patient mouth without need of water (or) chewing and release its content instaneously.

So, this dosage form is more comfortable for pediatric, geriatric and psychotic patients.

A fast dissolving tablet form would thus be advantage as water-soluble and preparation into dissolve rapidly and there by result in rapid absorption without any lag time.

5. Plan of work

The scheme of proposed work is as follows

1) Preformulation.
   - UV Analysis
   - IR Studies
2) Selection of Excipients
3) Drug-excipient compatibility studies
4) Selection of suitable granulation method.
5) Compression of tablets
6) Evaluation of physical and chemical parameters.
7) Evaluation of tablets.

Evaluation

1) Weight variation.
2) Hardness
3) Friability
4) Disintegration time
5) Dissolution study.
6) Uniformity of content
7) Wetting time
8) Stability studies

6. Drug and Excipients

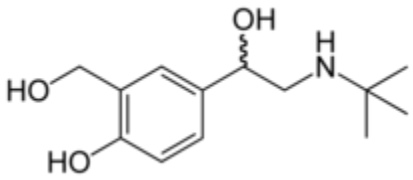
6.1 DRUG PROFILE[43,44,45,46]

Drug Name -Salbutamol sulphate

Classification -β_2 adrenergic agonist

Synonym -Albuterol sulphate

Chemical structure



H_2SO_4

Chemical Name - α1-[(tert-butylamino) methyl]-4-hydroxy-m-xylene- α,α'-diol sulfate

Molecular weight - 576.71

Molecular formula - $(C_{13}H_{21}NO_3)_2$ H_2SO_4

Description

Colour -White to almost white powder

Odour -Odourless

Solubility -Soluble in four parts of water

Slightly soluble in 96% ethanol

Melting point -155ºC

Optical rotation -Racemic mixture

Mechanism of action

Albuterol is a moderately selective β_2 -adrenergic agonist that stimulates receptors of the smooth muscle in the lungs, uterus, and vasculature supplying skeletal muscle. Albuterol is racemic beta-agonist, comprised of an equal mixture of R- and S-isomers. The R-isomer, known as levalbuterol, is primarily responsible for bronchodilation. Although not confirmed during clinical trials, the S-isomer of albuterol has bronchoconstrictive properties inanimalmodels.Intracellularly; the actions of albuterol are mediated by cyclic AMP, the production of which is augmented by β_2-stimulation. Albuterol is believed to work by activating adenylate cyclase, the enzyme responsible for generating cyclic AMP, an intracellular mediator. Increased cyclic AMP leads to activation of proteinkinase A, which inhibits phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. The net result of β_2-receptor agonist in the lungs is relaxation of bronchial and tracheal smooth muscles, which in turn relieves bronchospasm, reduces airway resistance, facilitates mucous drainage, and increases vitalcapacity.

Albuterol can also inhibit the degranulation and subsequent release of inflammatory autocoids from mast cells. Stimulation of β_2-receptors on peripheral vascular smooth muscle can cause vasodilation and a modest decrease in diastolic blood pressure. Albuterol is an effective adjunctive treatment for hyperkalemia; β_2-adrenergic stimulation results in intracellular accumulation of serum potassium due to stimulation of the Na/K ATPase pump, leading to moderate degrees of hypokalemia.

Pharmacokinetics

Albuterol can be administered as oral tablets or oral solution, but is more commonly administered by oral inhalation. Following oral inhalation, albuterol is absorbed over several hours from the respiratory tract. It is postulated from studies with other inhaled bronchodilators that most of an albuterol inhaled dose (approximately 90%) is actually swallowed and absorbed through the GI tract. Onset of bronchodilation occurs within 5—15 minutes after oral inhalation, peaks in 0.5—2 hours, and lasts 2—6 hours. Administration via nebulization does not appear to significantly alter the pharmacokinetics of albuterol. When administered orally, albuterol is well absorbed through the GI tract. Onset of action begins within 30 minutes, peak levels are reached in 2—3 hours, and duration of action is 4—6 hours for the conventional-release tablets and 8—12 hours for the sustained release product.

Albuterol crosses the blood-brain barrier and may cross the placenta. The liver metabolizes albuterol extensively to inactive compounds. Excretion of albuterol occurs through the urine and faeces. After oral inhalation, 80—100% of a dose is excreted via the kidneys within 72 hours; up to 10% may be eliminated in feces. After oral administration, 75% of a dose is excreted in urine within 72 hours as metabolites; 4% may be found in faeces. The elimination half-life of albuterol ranges from 2.7-5 hours, with orally administered albuterol having a shorter half-life than the inhaled product

Indications:

1. Bronchodilator for in asthma, chronic bronchitis, emphysema and other condition.

Contra indications.

1. Salbutamol preparations should not be used to manage threatened abortions.
2. Inhaled salbutamol is not appropriate for the managements of premature labour.
3. Hyper sensation to salbutamol

Adverse reaction:

Life- threatening effects:

Electro cardio graphic evidence of myocardial ischemia was reported in healthy pregnant women was reported.

Acute over dosage:

Overdose of albuterol between 5 to 240 mg produced no fatalities. The commonest symptoms are tremor, flushing, agitation and palpitation to tachycardia.

Severe (or) irreversible adverse effects:

(i) Ventricular ectopic beats have been reported during infusion of albuterol in one pregnant women.

(ii) Angina accompanied by ECG charges was reported in 3 patients with ischemic heart disease and either Asthma (or) copd during oxygen driver nebulization in hospital.

Symptomatic adverse effects:

It includes tremor, anxiety, muscle cramps, headache and palpitations

Drug dosage and administration:

Neonates: The drug is rarely in the neonatal period.

Children: Suitable and doses for children under 7 years are syrup / tablets 2 mg 3 times daily. Slow – release tablets 4 mg at night, respirator solution 1mg four times daily.

Pregnant women: It should be used in the first trimester unit essential.

Elder patients: Inability to use pressurized aerosol, Rotocaps may be needed oral or high doses more likely to provoke angina, cardiac arrymias (or) patients with prostatism, urinary retention.

Drug interactions:

Potentially hazardous interaction:

Treatment with diuretics may augment the hypokalemia that occurs with large doses of albuterol. Effects of albuterol are inhibited β_1 antagonist.

Potentially useful interactions:

The theoretical synergism of β_1 Stimulants and theophyline were as bronchodilators.

Table No.3 Salbutamol Sulphate Commercially Availed Product

S.No	Brand Name	Dose form	Dose Available	Company
1	Ventrolin	CR Capsule Syrup MDI	8mg 2mg/5ml 100 mcg/puft	GSK GSK GSK
2	Servent	Inhaler	50 mcg/ puff	GSK
3	Venmix	Syrup	2 mg / 5ml	Unimaek
4	Salbetol	Tablet	2mg 4mg	FDC
5	Salbid	tablet	2mg 4mg	Micro labs
6	Asthalin	tablet	2mg 4mg	cipla

6.2 EXCIPIENTS PROFILE

1. Saccharin sodium[47]

Synonyms: Soluble saccharin,
Sodium – o- benzo sulfamide soluble glucoside

Non- Proprietary Names:
USP: Saccharin sodium
BP: Saccharin sodium

Chemical Name: 1,2 Benzisothiazol – 3 (2H) – 1,1, dioxide, sodium salt
1,2 Benziso thiazolin – 3 cone)- 1,1, dioxide,
Sodium salt dehydrate (6155 – 57-B)
Anhydrous (128 – 44 – 9)

Description:

A white odorless (or) faintly aromatic, effervescent crystalline powder with intensity sweet taste, both forms of saccharin sodium (76% and 84%) are identical in the appearance.

2. Crospovidone[50]

Synonym Kollidon CL,
Kollidon CL – M,
Polyplasdone – XL,
Polyplasdone XL10

Chemical Name

1- Ethenyl-2- Pyrrolidinone homopolymer

Nonproprietary Names

BP- Crospovidone
USPNF- Crospovidone

Description

Crospovidone is white to creamy white finely divided, free flowing practically tasteless / nearly odorless, hygroscopic powder.

Functional Category

Tablet Disintegrant

Application in Pharmaceutical Formulation

Crospovidone is water insoluble tablet disintegrate and dissolution agent used at 2-5% concentration in tablet prepared by direct compression / wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency of crospovidone strongly influence disintegration of tablets.

Large particles provide a faster disintegration than smaller particles. Crospovidone can also be used as solubility enhancer with the technique of co- evaporation. It can be also used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovindone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

3. Sodium Starch Glycolate (SSG) [49]

Synonyms Carboxymethy1 starch (sodium salt),
Explotab,
Primojel.

Chemical Name

Sodium carboxymethy1 starch.

Nonproprietary Names

BP- Sodium starch glycolate.
USP NF- Sodium starch glycolate.

Description

Sodium starch glycolate is a white to off – white odorless, tasteless, free flowing powder. It consists of oval or spherical granules 30-100 micrometers in diameter with some less spherical granules ranging from 10-35 micrometer in diameter.

Applications

Sodium starch glycolate is widely used in oral pharmaceuticals as disintegrant in capsule and tablet formulation. It is commonly used in tablets prepared by either direct compression or wet granulation process. The usual concentration employed in formulation is between 2-8% with the optimal concentration of about 4%. Although in may case 2% is sufficient disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Although the effectiveness of many disintegrate is affected by the presence of hydrophobic excipients such as lubricant, the disintegrant efficacy of sodium starch glycolate is unimpaired by increasing the tablets compression pressure also appears to have no effect on disintegration time.

4. **Croscarmellose Sodium** [50]

Synonyms Ac- Di- Sol,
Cross – linked carboxy methylcellulose sodium, Primellose, solutab.

Chemical Names
Cellulose Carboxy Methy1 Ether, Sodium salt, cross- linked.

Description

Sodium starch glycolate is a white to off- white odorless, tasteless, free flowing powder. It consists of oval or spherical granules 30-100 micrometers in diameter with some less spherical granules ranging from 10-35 micrometer in diameter.

Applications

Sodium starch glycolate is widely used in oral pharmaceuticals as disintegrate in capsule and tablet formulation. It is commonly used in tablets prepared by either compression or wet granulation process. The usual concentration employed in formulation is between 2-8% with the optimal concentration of about 4%. Although is many cases 2% is sufficient disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Although the effectiveness of many disintegrant is affected by the presences of hydrophobic excipients such as lubricant, the disintegrant efficacy of sodium starch glycolate is unimpaired by increasing the tablets compression pressure also appears to have no effect on disintegration time.

5. Mannitol [52]

Synonym Cordypic acid, 1, 2, 3, 4, 5, 6. - Hexane hexol

Chemical Names.

D-mannitol

Nonproprietary Names

BP- Mannitol.

USP NF- Mannitol

Description

D- Mannitol is a hexahydric alcohol related to mannose and is isomeric with sorbitol. It is occurs as white, odorless, crystalline power, or free – flowing granules it has sweet taste, approximately as sweet as glucose and half sweet as sucrose. It imparts cooling sensation in mouth.

Application

Mannitol is widely used in pharmaceuticals formulations as sweetning agent. In pharmaceutical preparations, it primarily used as diluents. Due to its non hygroscopic nature. It may be used with moisture sensitive active ingredients. Mannitol is commonly used as excipients in manufacture of chewable tablet formulation because of its negative heat solution, sweetness and mouth feel.

6. Magnesium Stearate[53]

Synonyms Stearic acid magnesium salt,
Magnesium octadecanoate

Chemical Name

Octadecanoic acid magnesium salt

Nonproprietary Names

BP- Magnesium stearate
PhEur – Magnesli stearate
USPNF- Magnesium stearate

Description

Magnesium stearate is a fine, white, precipitated, milled impalatable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to touch and readily adheres to skin.

Applications

Magnesium stearate is widely used in cosmetics, foods, and pharmaceuticals. It is primarily used as lubricant in capsule and tablet manufacture at concentration between 0.25-50% concentrations.

7. Povidone

Non-proprietary Name Povidone

Functional Category Tablet binder
Suspending agent

Synonyms Polyvidone, Polyvinylpyrolidine, PVP, Kollidon, Plasdone.

Chemical Name 2-pyrrolidinone, 1, ethyl homopolymer-1- vinyl-2- pyrrollidionone polymer

Typical properties

Density 1.17 to 1.18 gm/cm^3

Solubility Readily soluble in water up to 60 %, freely soluble in many organic solvents

Table No.4
Application of Povidone in Pharmaceutical Formulation

S.No	Use	Concentration
1.	Carrier for drug	10 - 25 %
2.	Dispersing agent	Up to 5 %
3.	Suspending agent	Up to 5 %
4.	Tablet binder, diluents, coating agent	0.5 - 5 %

7. MATERIALS AND METHODS

7.1 List of Instruments Used

Table No.5

S. No	Instrument Name	Company
1.	Digital weighing balance	Sartorius
2.	Tray drier	Mixofill
3.	Rotary tablet punching machine	Rimeck minipress
4.	pH Meter	Thermovorision
5.	Tap density tester	Electrolab
6.	Mechanical sieve shaker	Retsch
7.	Friability tester	Roche
8.	Hardness tester	Pfizer
9.	UV-Visible spectrophotometer	Shimandzu
10.	Dissolution tester USP	Electrolab
11	Environment Chamber	Heco

7.2 List of Exponents and Chemical Used

Table No.6

S.No	Instrument Name	Company
1	Sodium starch glycolate	Ranchem, Ranbaxy
2	Cros- povidone	Ranchem, Rambaxy
3	Cros- carmellose sodium	Ranchem, Ranbaxy
4	Poly- vinyl pyrrolidine	FMC, Germany
5	Isopropyl alcohol	Microfine chemicals
6	Mannitol	BASF Germany
7	Sodium saccharin	Rankem, ranbaxy
8	Magnesium sterate	Ranchem lab chemicals
9	Talc	Nice chemical Pvt limited
10	Orange flavour	IFF Ltd,Chennai
11	Lactose monohydrale	Lactose, India

7.3 PREFORMULATION STUDIES

IDENTICATION AND CHARACTERIZAITON OF SALBUTAMOL SULPHATE

Infra-Red Absorption spectrum

The IR spectrum of salbutamol was determined and recorded using IR Spectro photometer. The KBr pellet method was used for preparation of salbutamol sample

.

UV Spectrophotometer method

Weigh accurately 10 mg of pure salbutamol drug was taken and dissolved in 100ml of water. This made up to 100 mcg/ ml solution. From this stock solution from 0.5ml was taken and diluted with phosphate buffer pH 6.2 up to 10 ml. then absorbance was measured at 276 nm using UV – spectrophotometer.

Melting point

The melting point of salbutamol was determined by capillary method.

7.4 Standard Curve for Salbutamol Suphate in Sorenson's Buffer Solution pH 6.2 [56]

Materials

- Salbutamol Sulpahate
- Sorenson's Buffer Solution pH 6.2

Procedure

100 mg of salbutamol was accurately weighted and then dissolved in 100 ml of water. This solution is having concentration 100 mg / ml. From this stock solution 50, 100,150,200,250,300 mg/ml by diluting phosphate buffer 6.2 pH. Absorbance was measured at 276 nm using UV-spectrophotometer (Shimadzu) Graph is plotted for absorbance UV concentration.

Table No.7 Standard Curve for Salbutamol Suphate

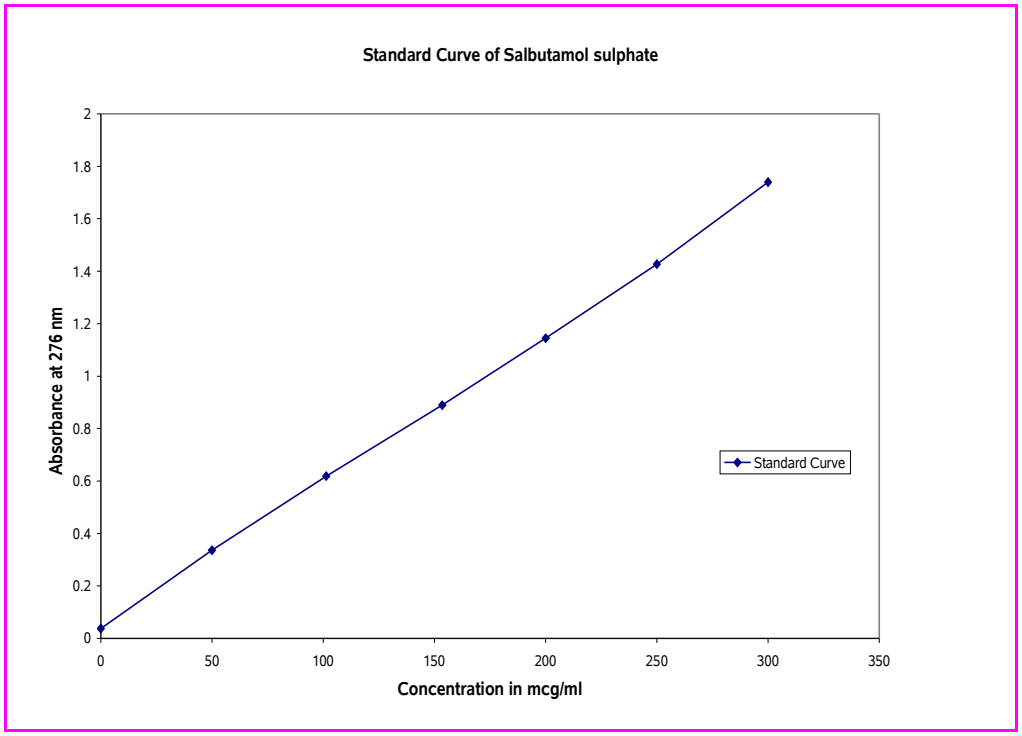
S.No	Concentration in mcg/ml	Absorbance at 276 nm
1	50	0.336
2	100	0.580
3	15	0.889
4	200	1.145
5	250	1.427
6	300	1.740

R - 0.9994

A - 0.0378

B - 0.0056

Figure No.1 Standard Curve for Salbutamol Suphate



Solubility[66]

The approximate solubility's of substance are indicated by the descriptive terms in the accompanying table.

Table No.8

Descriptive term	**Parts of solvent require for 1 Part of solute.**
1. Very soluble	Lees than 1
2. Freely soluble	From 1 to 10
3. Soluble	From 10 to 30
4. Sparingly soluble	From 30 to 100
5. Slightly soluble	From 100 to 1,000
6. Very Slightly soluble	From 1,000 to 10,000
7. Practically insoluble (or) Insoluble	Greater than (or) equal to 10,000.

7.5 Selection of Exicipients

Table No.9

Name of the Substance	Use in formulation
1. Salbutamol sulphate	Drug
2. Lactose monohydrate	Diluent
3. Mannitol	Diluent
4. Sodium Starch glycolate	Super Disintegrant
5. Cros- povidone	Super Disintegrant
6. Cros- carmellose sodium	Super disintegrant
7. Sacharin sodium	Sweetning agent
8. Povidone	Binder
9. Orange flavours	Flavoluring agent
10. Magnesium sterate	lubricant
11. Talc	Anti adhesive.

Formulation of salbutamol sulphate mouth dissolving tablets using super disintegrants

The tablet consisted of drug, mannitol, orange flavour, magnesium state, talc and various concentrations of lactose mono hydrate and super disintegrants. The weight of tablet batch was kept constant. All the batches of 50 tablets were prepared by wet granulation process using 10- station Rotatory tablet punching machine.

Control Formulation (Formulation with out super disintegrants)

Table No.10

S.No	Ingredients	Quantity F1 (mg)
1.	Salbutamol Sulphate	4
2.	PVP	3
3.	Mannitol	30
4.	Sodium saccharin	1
5.	Orange flavour	1.5
6.	Lactose mono hydrate	110.5mg
7.	Total	150

7.6 DESIGN OF FORMULATION

Table No.11 Formulation of Tablet Containing Sodium Starch Glycolate as Super disintegrants

S.No	**Name of Ingredients**	**Quantity**	**(mg)**
		F2	F3
1.	Salbutamol sulphate	4	4
2.	Sodium starch glycollate	12	15
3.	PVP	3	3
4.	Mannitol	30	30
5.	Saccharin sodium	1	1
6.	Orange flavour	1.5 mg	1.5 mg
7.	Lactose	98.5	97
8.	Total	150	150

Table No.12 Formulation of Tablet Containing Crospovidone as Super Disintegrant

S.No	Name of Ingredients	Quantity (mg) F4	F5
1.	Salbutamol sulphate	4	4
2.	Sodium starch glycollate	12	15
3.	PVP	3	3
4.	Mannitol	30	30
5.	Saccharin sodium	1	1
6.	Orange flavour	1.5	1.5
7.	Lactose	98.5	97
	Total	150	150

Design of formulation cros – carmuellose sodium as a super disintegrants

Formulation of tablet containg cros – carmulose sodium as a superdisintegrants.

Table No.13

S.No	Name of Ingredients	Quantity (mg) F6	F7
1.	Salbutamol sulphate	4	4
2.	Sodium starch glycolate	12	15
3.	PVP	3	3
4.	Mannitol	30	30
5.	Saccharin sodium	1	1
6.	Orange flavour	1.5 mg	1.5 mg
7.	Lactose	98.5	97
	Total	150	150

7.7 Evaluation of Fast Dissolving Tablets[65]

Preformulation studies

Angle of repose

With care, dynamic angle of repose measurement can be replicated with relative standard deviation of approximately 2% they are particularly sensitive to change in particle size distribution and to moisture content and they provide rapid means of monitoring significant batch difference in these respells.

$$\Theta = \tan^{-1} h/r$$

Where,

Θ - Angle of repose

H-Height of the pile

R- Radius of the base of the conical pile

Angle of repose was determined by using funnel method. Powder was paired from a funnel that can be raised vertically until a maximum cone heights, it was obtained. Diameter of heap, d was measured.

The angle of repose calculated by above formula

.

Table No.14 Angle of Repose as indicating of powder flow – properties

Angle of repose (Degrees)	Types or flow
<20	Excellent
20.30	Good
30.34	Passable
>40	Very poor

Bulk Density [66]

Bulk density is of great importance when one considers the size of high dose capsule product (or) me homogeneity of how dose formulation in which where is large difference in drug and Excipients densities. Apparent bulk density is determined by pouring pre sieved (40 sieve) bulk drug into a graduated cylinder via a large and measuring the volume and weight "as it as".

Powder flow properties [64]

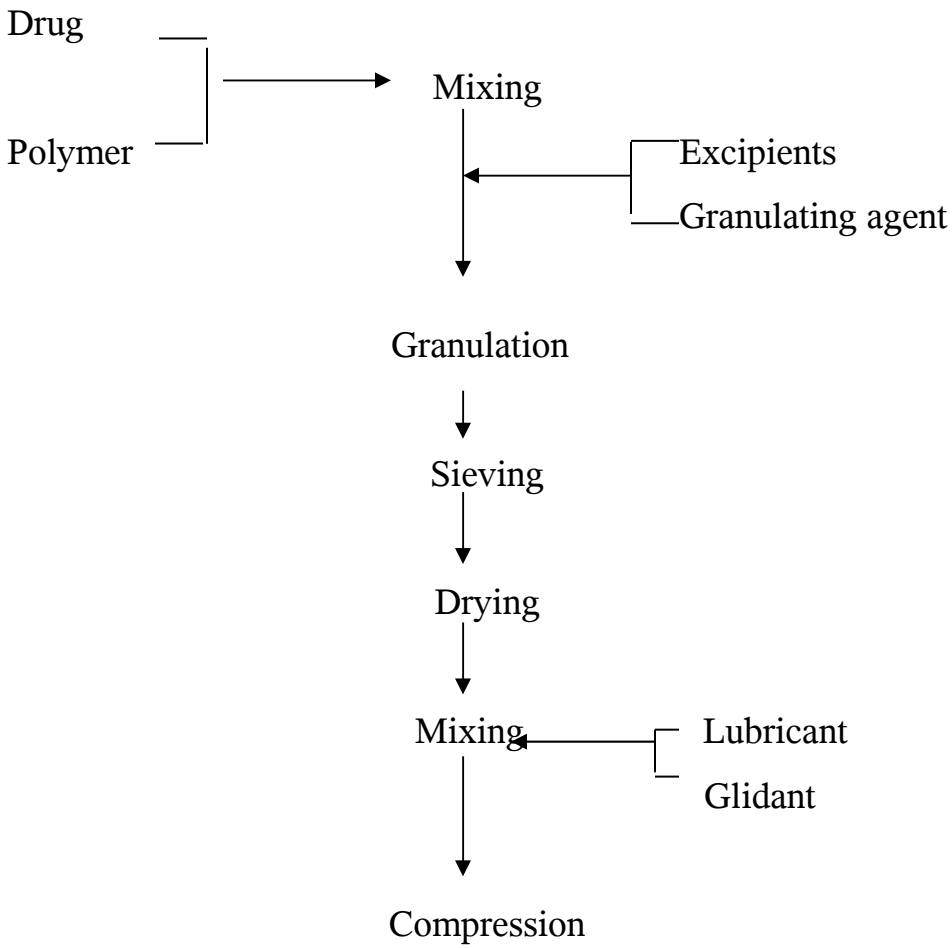
One of the ways of measurement of free flowing ability of powder is compressibility.

Carr's index = (Vi-Vt)/Vi X100

Vi = Tapped density

Vt = Initial bulk density

Process chart



Evaluation of tablets

Weight variation

Weight of 20 tablets was determined. Form that average weight was calculated. Then individual tablet were weighed and the individual weight was compared with the average weight.

Specification as IP

Table No.15

S.No	Average weight of the tablets	Percentage deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250mg or more	5

Hardness

Although there is no official test for tablet hardness this property must be controlled during production to ensure that the product is firm enough to withstand handling without breaking, chipping etc., the hardness of a tablet is indicative of its tensile strength and is measured in term of pressure required to crush it when placed on its edge. Hardness of about 5 kg/cm^2 is considered to be minimum for uncoated tablets for mechanical stability. The hardness had influence on disintegration and dissolution times. Hardness is the factor that affects the bioavailability.

Friability

Friability generally refers to loss in weight of tablets in the container due to chipping, abrasion, and erosion. The standard device available is "Friabilators" (Consist of circular plastic chamber, a divided into two compartments. The chamber rotates at a speed of 25 r.p.m and drops tablets by distance of 15 cm). The weight loss should not be more than one percent.

Formula

Percentage Friability = (initial weight-final weight/initial weight) X 100

Procedure

10 tablets are weighed and transferred in to Friabilator. Then after 100 revolutions per minute the tablets were unloaded and weight of the tablets was noted. The difference should not exceed one percent.

Disintegration time

Tablet was added to 100 ml distilled water at 37ºC± 0.5 ºC. Time required for complete dispersion of a tablet was measured win help of digital tablet disintegration test apparitions.

Uniformity of content:

.

Procedure

Crush two tablets, taken the powder equivalent of dose 10mg, add 100 ml ethanol (100mg/ml). Take 0.5ml and diluted with phosphate buffer 6.2 PH (0.5mg/ml) and it was filtered; measure the absorbance of resulting solution at 276 nm using UV- spectro photometric ally.

Dissolution study

Dissolution rate was studied by using USP type II apparatus under following experimental condition

- 50 rpm
- 900 ml Phosphate buffer 6.2 Sorenson's sodium
- 37± 0.5 ^{o}C as a temperature of dissolution medium.

Aliquot equal to 5rnl of dissection medium was withdrawn of specific time interval and it was filtered. Absorption of filtered solution was checked by 276 nm and drug content was determined from standard calibration curve.

In vitro **dispersion time**

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of pH 6.8 (simulated saliva fluid). There tablets from each formulating were randomly selected and vitro dispersion time was preformed

Wetting time:

The method was followed to measure tablet – wetting time a price of tissue paper folder twice was placed in small pertidish (6.5cm) containing 6ml of simulated saliva pH a tablet put on the paper, and the time for complete wetting was measured. 3 trials of each batch were performed and standard deviation was also determined.

7.8 ACCELERATED STABILITY STUDIES

Stability

Stability is officially defined as the time lapse during which the drug product retains the same properties and characteristics that it possessed at the time of manufacture. This process begins at early devolvement phases.

. Instability in modern formulation is often detectable only after considerable storage period under normal condition. To assess the stability of a formulated product its usual to expose it to high stress conditions to enhance its detoriation and therefore the time required for testing is reduce common high stress like temperature and humidity. This will eliminate unsatisfactory formulation.

Strategy of stability testing

1. The study of drug decomposition kinetics
2. The development of stability dosage form.
3. Establishment of expiration date for commercially available drug product is some of the needs of stability testing.

4. Data form stability studies should be provided on at least three primary batches of the drug product.
5. The batches should be manufactured to a minimum of pilot scale.
6. Important point of view of the safety of the patient, patient relieves a uniform dose of drug throughout the shelf life of the product.

The Stability Storage condition

Table No.16

S.No	Study	Storage condition	Minimum period
1.	Long-term study	25° C ± 2° C 60 % ± 5% RH	12 month
2.	Intermediate study	30 ° C ± 2° C 60 % ±5 % RH	6 month
3.	Accelerated study	40° C ± 2 ° C 75% ±5 % RH	6 month

Procedure

Selected batches were placed in a high density polyethylene container, blister pack, stripe pack etc. they are kept in stability chamber maintained at 40°C and 75 % RH. The stability studies were carried out for a period of one month. The tablets were tested and checked for the above mention specification.

8. Results and Discussion

Preformulation Studies

Drug identification – by Spectrophotometer method (UV)

Table No.16 UV- Absorbance of Salbutamol sulphate in 0.1 N HCL

S. No	Concentration	Absorbance at 276nm
1	300 mcg/ml	1.673

Table No.17 UV-Absorbance of Salbutamol Sulphate in water

S. No	Concentration	Absorbance at 276 nm
1	300 mcg/ml	1.621

Discussion

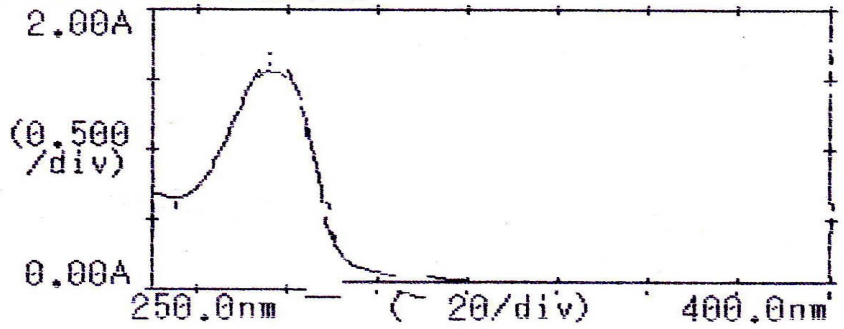
- The UV- absorbances of the Salbutamol sulphate were performed at different concentration in different medium and their wavelength were found and compared with monograph.

FigureNo.2 UV- Absorbance of Salbutamol sulphate in 0.1 N HCL

Peak
276.0 1.621

Valley
255.5 0.664

12/Oct/07 00:21:20
Data Processing



12/Oct/07 00:22:00
Point pick

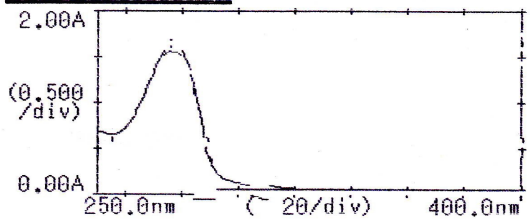
	Abscis.	Ordinat.		Abscis.	Ordinat.
1	300.0	0.137	11	280.0	1.571
2	298.0	0.151	12	278.0	1.608
3	296.0	0.170	13	276.0	1.621
4	294.0	0.205	14	274.0	1.587
5	292.0	0.278	15	272.0	1.480
6	290.0	0.423	16	270.0	1.335
7	288.0	0.664	17	268.0	1.188
8	286.0	0.971	18	266.0	1.046
9	284.0	1.255	19	264.0	0.912
10	282.0	1.465	20	262.0	0.803

Figure No. 3 UV-Absorbance of Salbutamol Sulphate in water

Peak
276.0 1.621

Valley
255.5 0.664

12/Oct/07 00:21:20
Data Processing



12/Oct/07 00:22:00
Point pick

	Abscis.	Ordinat.		Abscis.	Ordinat.
1	300.0	0.137	11	280.0	1.571
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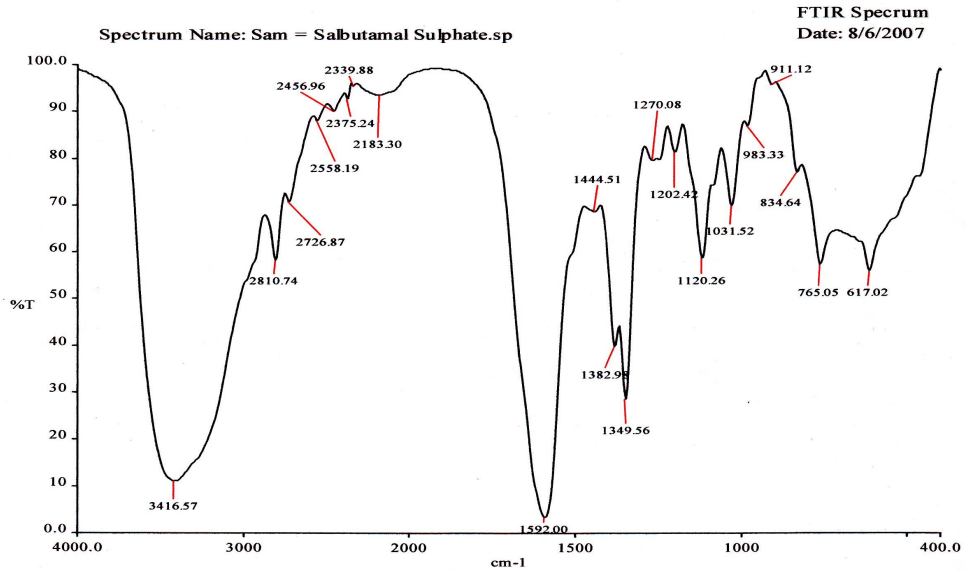
7	288.0	0.664	17	268.0	1.188
8	286.0	0.971	18	266.0	1.046
9	284.0	1.255	19	264.0	0.912
10	282.0	1.465	20	262.0	0.803

Figure No.4 IR Spectrum of Salbutamol Sulphate

ACIC
St.Joseph's College (Autonomous)
Trichy-2



Sam = Salbutamal Sulphate.pk

SAM_SA~1.SP 3601 4000.00 400.00 3.42 99.15 4.00 %T 3 0.50

REF 4000 99.15 2000 97.98 600
3416.57 11.11 2810.74 58.19 2726.87 70.74 2558.19 88.07 2456.96 90.00
2375.24 92.77 2339.88 95.35 2183.30 93.52 1592.00 3.42 1444.51 68.51
1382.98 39.69 1349.56 28.64 1270.08 79.47 1202.42 81.25 1120.26 58.63
1031.52 69.80 983.33 86.81 911.12 95.60 834.64 76.97 765.05 57.26
617.02 55.85

S.No	Wave Number in cm^{-1}	Functional Group
1	31275	OH and NH Stretching
2	2797	-CH Aliphatic
3	2454	-CH for – CH_2 - Chain
4	1616	Aromatic ring C= C Stretching
5	1442	OH Phenolic Stretching
6	1118	Aromatic CH Bending
7	1389	S=O Asymmetric

Discussion

- The structure of Salbutamol sulphate was confirmed by IR spectrum and the spectrum was compared with standard graph in monograph.

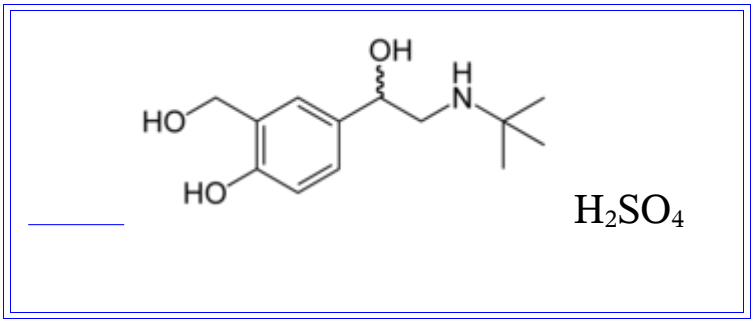
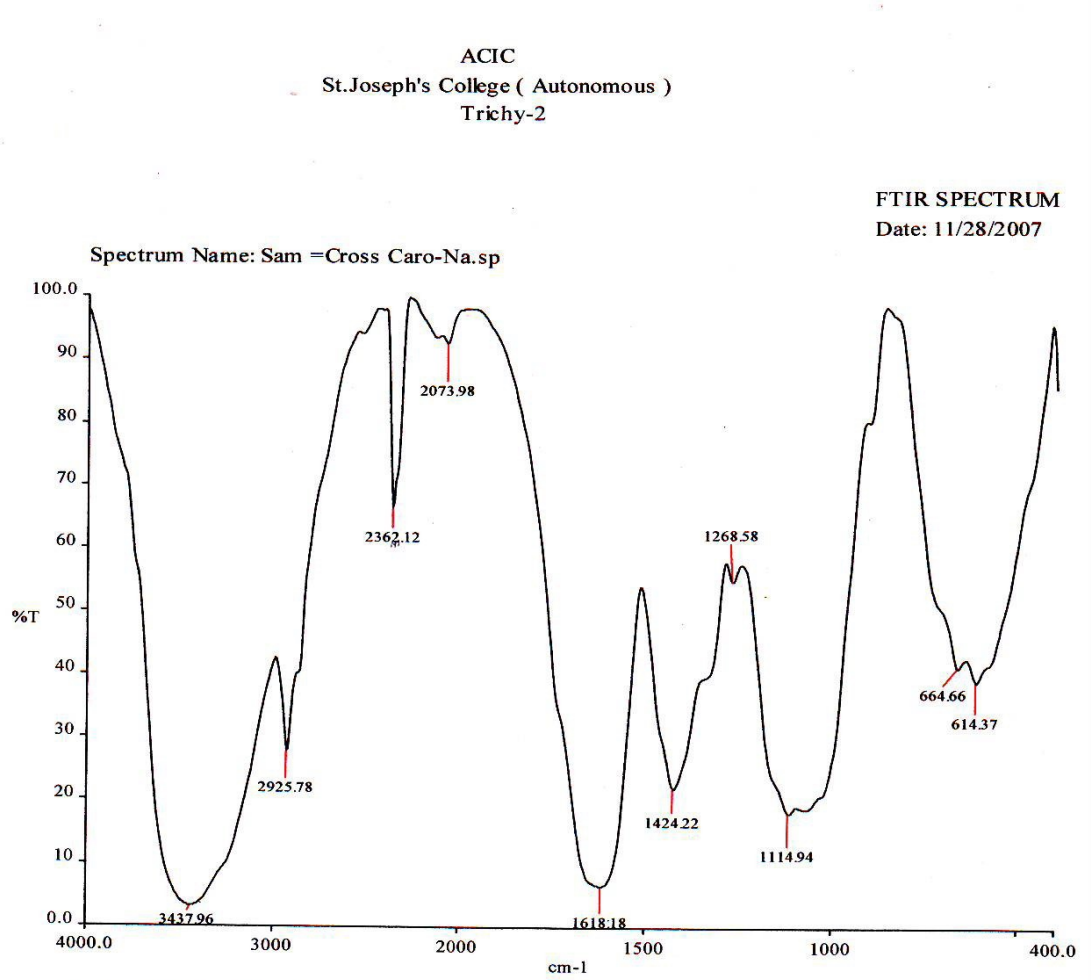


Figure.No.5 IR Cros-Carmellose Sodium



Sam =Cross Caro-Na.pk

SAM_CR~1.SP 3601 4000.00 400.00 3.17 99.79 4.00 %T 5 1.00

REF 4000 97.77 2000 97.85 600
3437.96 3.17 2925.78 27.88 2362.12 66.39 2073.98 92.51 1618.18 6.56
1424.22 21.92 1268.58 54.67 1114.94 17.97 664.66 41.05 614.37 38.82

Infra-Red Spectrum

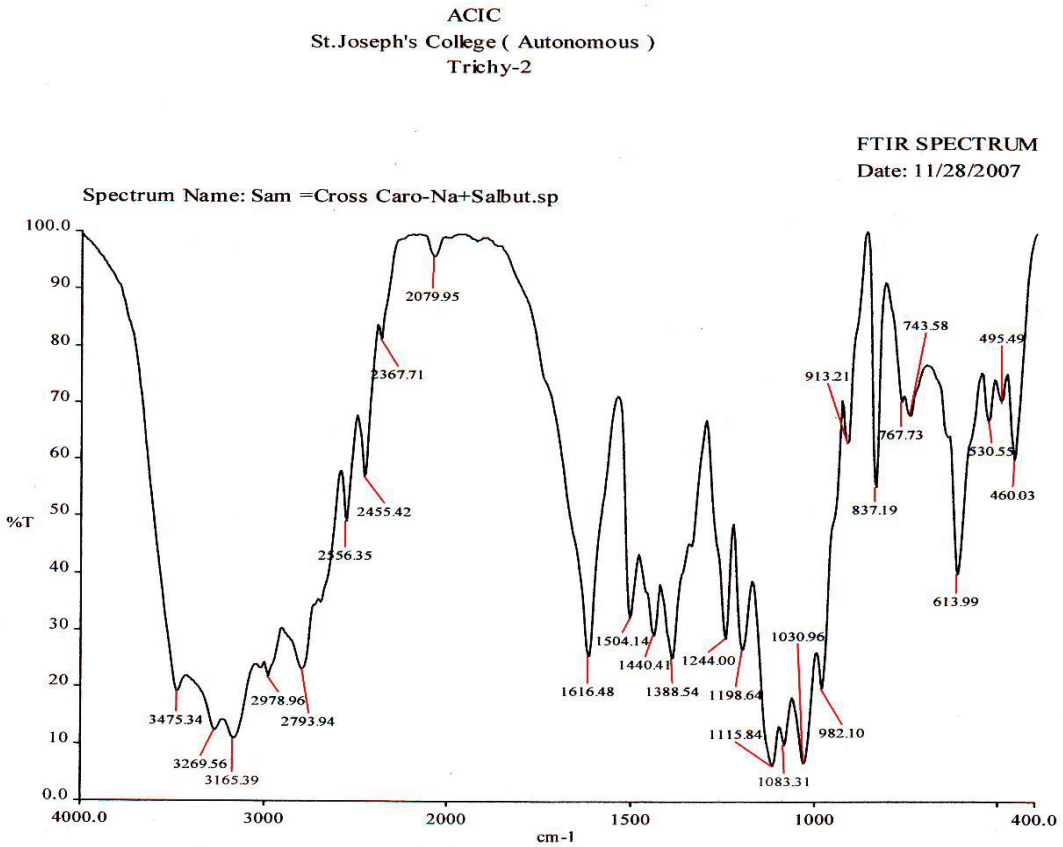
Table No.20 IR Cros-Carmellose Sodium

S.No	Wave Number in cm^{-1}	Functional Group
1	3437	-OH/NH Stretching
2	2925	-CH Aliphatic Stretching
3	2362	-CH (– CH_2 -) Stretching
4	1618	C=C Aromatic Stretching
5	1424	OH Phenolic Stretching
6	1268	C-O-C Ether Stretching
7	1114	Ar –O–CH_2 Stretching

Discussion

- The structure cros-carmellose sodium of was confirmed by IR spectrum.

Figure No.6 IR Spectrum of Salbutamol Sulphate + Cros-Carmellose Sodium



Sam =Cross Caro-Na+Salbut.pk

SAM_CR~2.SP 3601 4000.00 400.00 6.30 100.00 4.00 %T 5 1.00

REF 4000 99.55 2000 98.91 600

3475.34	19.27	3269.56	12.43	3165.39	10.94	2978.96	21.96	2793.94	23.13
2556.35	49.14	2455.42	56.91	2367.71	81.31	2079.95	95.67	1616.48	25.54
1504.14	32.21	1440.41	29.20	1388.54	25.17	1244.00	28.66	1198.64	26.63
1115.84	6.30	1083.31	9.92	1030.96	6.62	982.10	19.78	913.21	62.93
837.19	55.13	767.73	70.20	743.58	67.74	613.99	39.91	530.55	66.71
495.49	70.08	460.03	59.84						

Infra-Red Spectrum

Table No.21 IR Spectrum of Salbutamol Sulphate + Cros-Carmellose Sodium

S.No	Wave Number in cm^{-1}	Functional Group
1	31275	OH and NH Stretching
2	2797	-CH Aliphatic
3	2454	-CH for – CH_2 - Chain
4	1616	Aromatic ring C= C Stretching
5	1442	OH Phenolic Stretching
6	1118	Aromatic CH Bending
7	1389	S=O Asymmetric

Discussion

- All peaks of Salbutamol sulphate are present in the mixture of cros-carmellose sodium and salbutamol sulphate; it shows the compatibility of Salbutamol sulphate with cros-carmellose sodium.

Solubility Studies

- Freely Soluble in the water
- Slightly soluble in 95% Ethanol

Melting point 155° C

Active pharmaceutical Consideration

Table No.22 Powder Properties of Formulation Containing Super Disintegrants

Formulation code	***Bulk density** gm/cm^3	***Angle of repose**	**Carr's index %**	**Type of flow**
F1	0.333	21° 41'	15.62	Excellent
F2	0.348	21° 43'	11.90	Excellent
F3	0.375	21° 20'	12.12	Excellent
F4	0.352	24° 09'	14.02	Excellent
F5	0.353	21° 43'	17.00	Good
F6	0.344	20° 10'	15.62	Excellent
F7	0.354	20° 57'	14.70	Excellent

* Average value of three observations.

Discussion

- The values of angle of repose and Carr's index were less than 25° and 15 % respectively, hence the flow properties of all formulations complied within the limits.

Evaluation of Mouth Dissolving Tablets

Table No.23 Tableting Properties of Control Formulation and Formulation Containing Sodium Starch Glycolate as a Superdisintergrants (8% And 10%)

S.No	Formulation Properties	F1(Control)	F2	F3
1	Weight variation %	1.431	1.318	1.385
2	Hardness in kg/cm^2	3.9±0.63	3.4±0.32	3.2±0.30
3	Friability %	0.252	0.318	0.398
4	Uniformity of content	98.65	98.07	98.17
5	Disintegration time in sec	162±1.48	59±2.70	49±4.1
6	Wetting time in sec	141±1.0	35.6±2.40	26.6 ±2.26

Discussion

- By comparing the properties of the control tablet with other tablets prepared by using various superdisintegrants, it was found that the control tablets had greater hardness and disintegration time due to absence of the superdisintegrants in the control formulation.
- The control formulation had also shown least friability.
- All physical parameters of the prepared tablets compile with monograph (Indian Pharmacopoeia)

Table No.24 Tableting Properties of Control Formulation and Formulation Containing Crospovidone as a Superdisintegrants (8% and 10%)

S.No	Formulation Properties	F1(Control)	F4	F5
1	Weight variation %	1.431	1.366	1.358
2	Hardness in kg/cm^2	3.9±0.63	3.7±0.01	3.5±0.63
3	Friability %	0.252	0.398	0.318
4	Uniformity of content	98.65	99.05	98.45
5	Disintegration time in sec	162±1.48	60± 0.77	55± 1.0
6	Wetting time in sec	141±1.0	13.3 ±1.65	11.0 ±1.0

Discussion

- By comparing the properties of the control tablet with other tablets prepared by using various superdisintegrants, it was found that control tablets had greater hardness and disintegration time due to absence of the superdisintegrants in the control formulation.
- The control formulation had also shown least friability.
- All physical parameters of the prepared tablets compile with monograph (Indian Pharmacopoeia).
- As the concentration of the crospovidone increases the disintegration time decreases.

Table No.25 Tableting Properties of Control Formulation and Formulation Containing Cros-Carmellose sodium as a Superdisintegrants (8% And 10%)

S.No	Formulation Properties	F1(Control)	F5	F6
1	Weight variation %	1.431	1.358	1.363
2	Hardness in kg/cm^2	3.9±0.63	3.3±1.18	3.5±0.63
3	Friability %	0.252	0.387	0.376
4	Uniformity of content	98.65	99.01	99.20
5	Disintegration time in sec	162±1.48	50±1.0	42±0.77
6	Wetting time in sec	141±1.0	17.6±1.74	16.3±1.28

Discussion

- By comparing the properties of the control tablet with other tablets prepared by using various superdisintegrants, it was found that control tablets had greater hardness and disintegration time due to absence of the superdisintegrants in the control formulation.
- The control formulation had also shown least friability.
- All physical parameters of the prepared tablets compile with monograph (Indian Pharmacopoeia).
- As the concentration of the cros-carmellose sodium increases the disintegration time decreases.

***In vitro* Drug Release**

Dissolution profile for mouth dissolving tablets containing salbutamol sulphate prepared by using Sodium Starch Glycolate in Sorenson's buffer (pH 6.2)

Table No.26 *In vitro* Drug Release

Time in minutes	%Drug Release F1 (Control)	% Drug Release F2	%Drug Release F3
2	-	36.96	40.98
4	-	40.98	53.03
6	-	49.00	65.08
8	-	53.03	85.17
10	-	57.05	89.19
12	-	65.08	89.19
14	-	69.10	-
16	-	77.16	-
18	-	81.16	-
20	-	81.16	-
22	-	-	-
24	-	-	-
26	-	-	-
28	-	-	-
30	-	-	-
32	-	-	-
34	0.80	-	-
36	4.80	-	-
38	12.85	-	-
40	20.79	-	-
42	24.91	-	-
44	28.92	-	-
46	32.94	-	-
48	36.96	-	-
50	40.98	-	-
52	49.00	-	-
54	53.03	-	-
56	57.07	-	-
58	65.08	-	-
60	69.10	-	-

Discussion

- Dissolution behaviour of controlled tablet has shown in table no.26 and figure no.1 and it was observed that controlled tablets has shown 69 percent drug release at 60 th minute and the drug was not completely released due to absences of superdisintegrants in the formulation.

- Dissolution profile of mouth dissolving tablets containing salbutamol sulphate by using sodium starch glycolate has shown in table no.26 and figure no.2 and 3 it was observed that the tablet containing 8 percent (F2) and 10 percent (F3) sodium starch glycolate had shown the drug release 81.16 percentage and 89.19 percentage respectively at 20 th and 12 th minutes, from the result that inferred with increase in the concentration of sodium starch glycolate and drug release was also rapid.

Figure No.7 *In vitro* Drug Release for control formulation

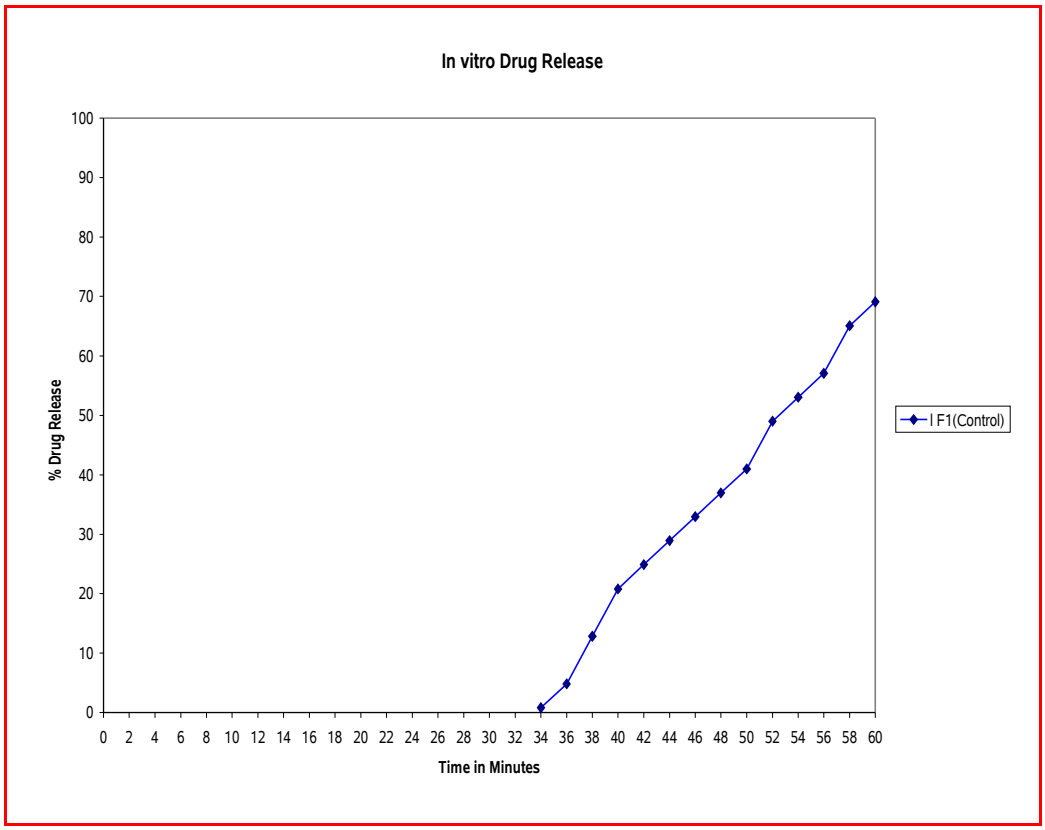


Figure No.8 *In vitro* Drug Release for F2 Formulation

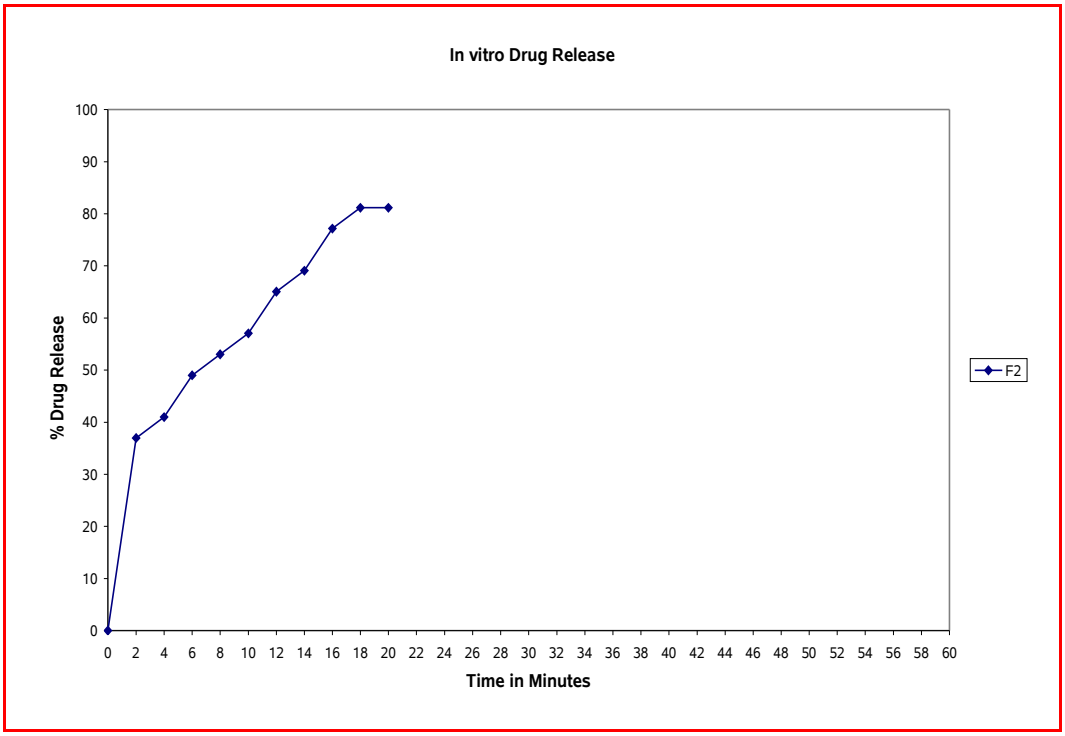


Figure No.9 *In vitro* Drug Release for F3 Formulation

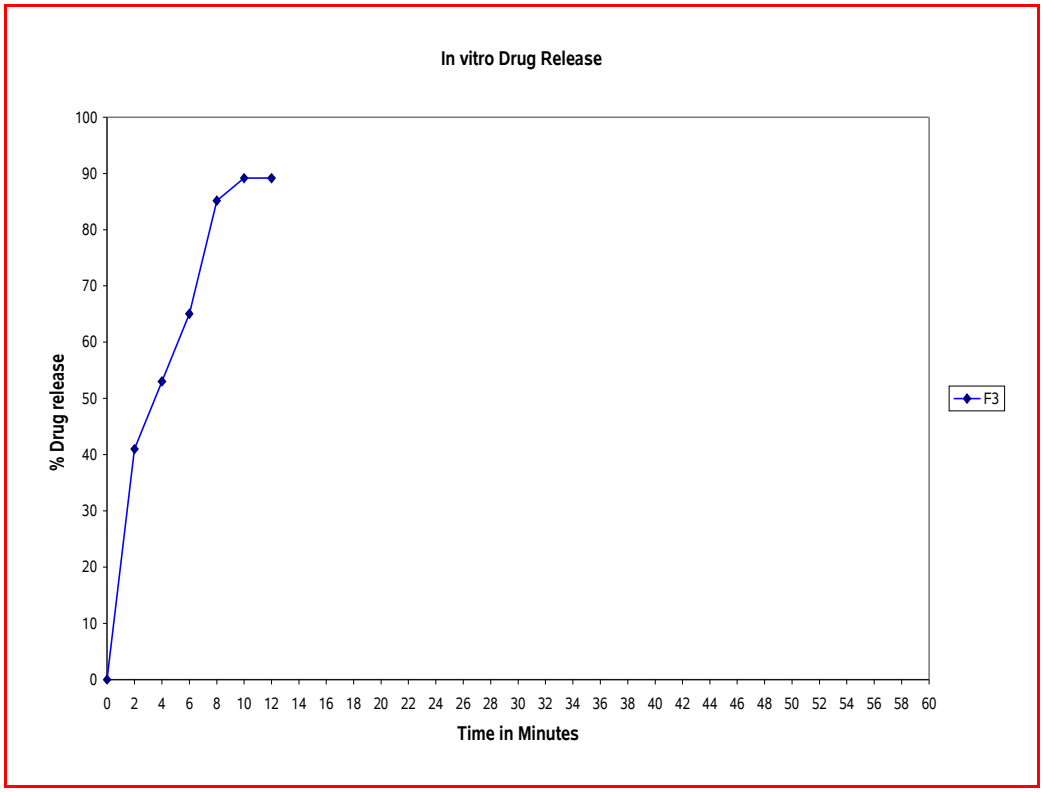


Figure No.10 Comparative *In vitro* Drug Release for F1, F2 and F3

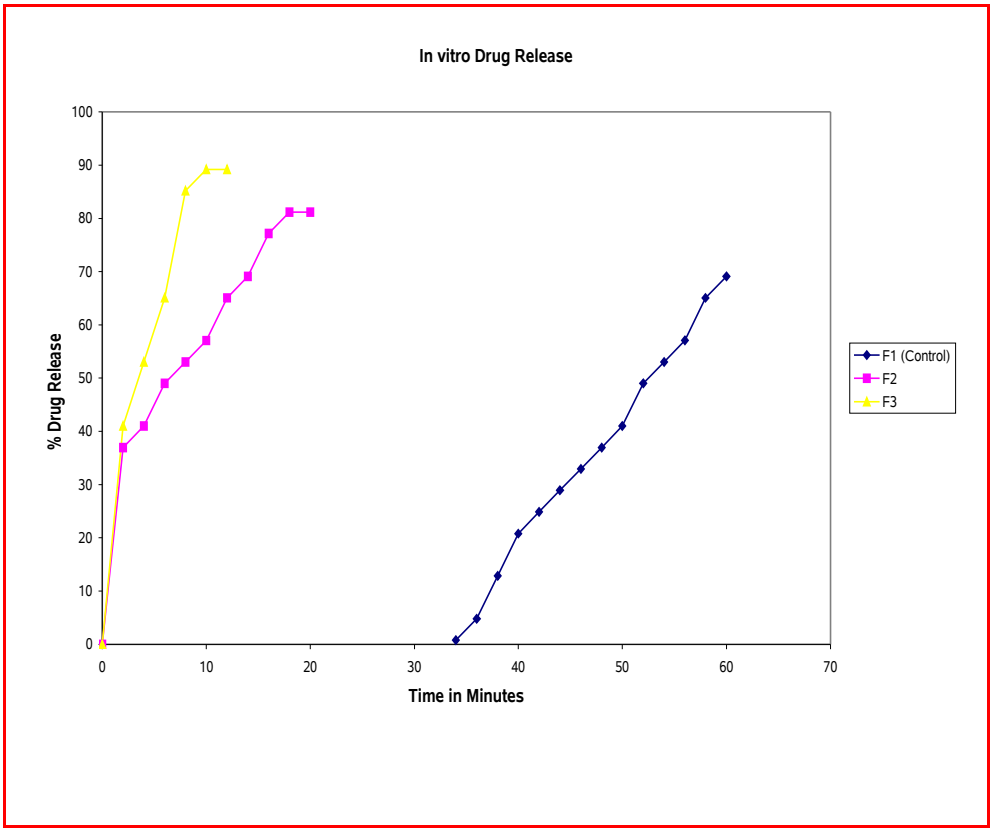


Table No.27 *In vitro* Drug Release

Dissolution profile for mouth dissolving tablets containing salbutamol sulphate prepared by using Crospovidone in Sorenson's buffer (pH 6.2)

Table No.27 *In vitro* Drug Release

Time in minutes	% Drug Release F1 (Control)	% Drug Release F4	% Drug Release F5
2	-	32.94	49.00
4	-	40.98	57.05
6	-	53.03	69.10
8	-	65.08	89.19
10	-	77.16	93.20
12	-	89.19	93.20
14	-	89.19	-
16	-		-
18	-		-
20	-		-
22	-	-	-
24	-	-	-
26	-	-	-
28	-	-	-
30	-	-	-
32	-	-	-
34	0.80	-	-
36	4.80	-	-
38	12.85	-	-
40	20.79	-	-
42	24.91	-	-
44	28.92	-	-
46	32.94	-	-
48	36.96	-	-
50	40.98	-	-
52	49.00	-	-
54	53.03	-	-
56	57.07	-	-
58	65.08	-	-
60	69.10	-	-

Discussion

- Dissolution behaviour of controlled tablet has shown in table no.27 and figure no.1 and it was observed that controlled tablets has shown 69 percent drug release at 60 th minute and drug was not completely released due to absences of superdisintegrant in the formulation.

- Dissolution profile of mouth dissolving tablets containing salbutamol sulphate by using crospovidone has shown in table no.27 and figure no.4 and 5 it was obsever that the tablet containing 8 percent (F4) and 10 percent (F5) crospovidone had shown the drug release 89.19 percentage and 93.20 percentage respectively at 14 th and 12 th minutes, from the result that inferred that drug release increases with increase in the concentration of crospovidone comparing with sodium starch glycolate,the drug release was rapid.

Figure No.1 1 *In vitro* Drug Release for F4 Formulation

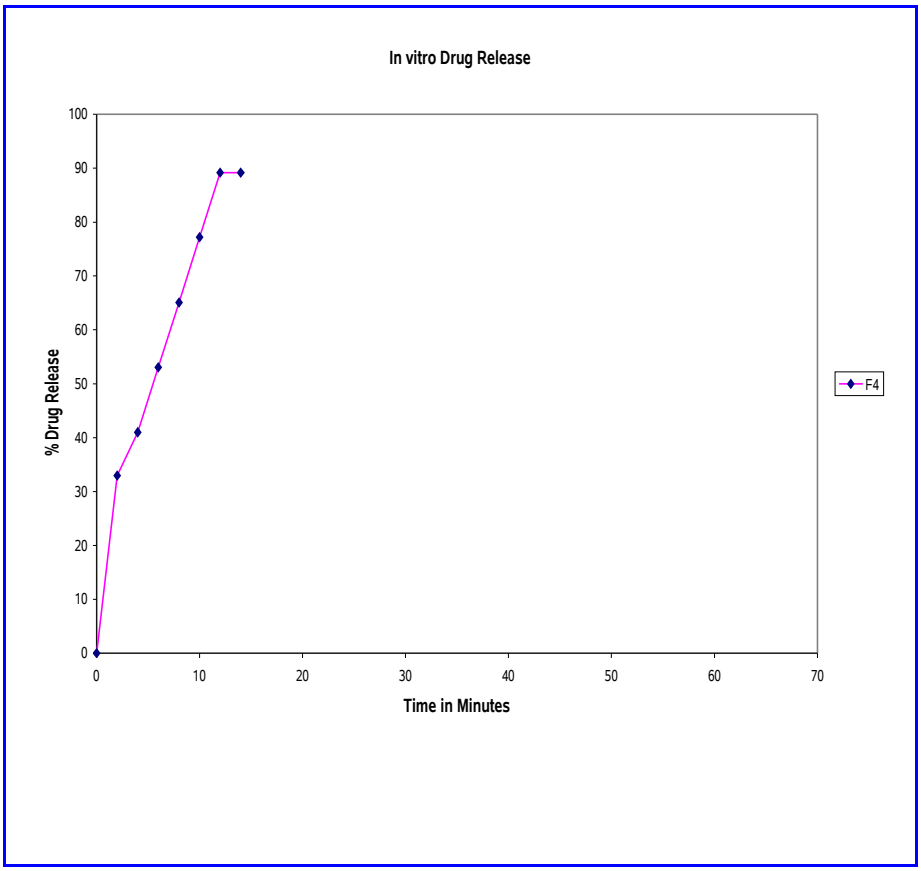


Figure No.12 *In vitro* Drug Release for F5 Formulation

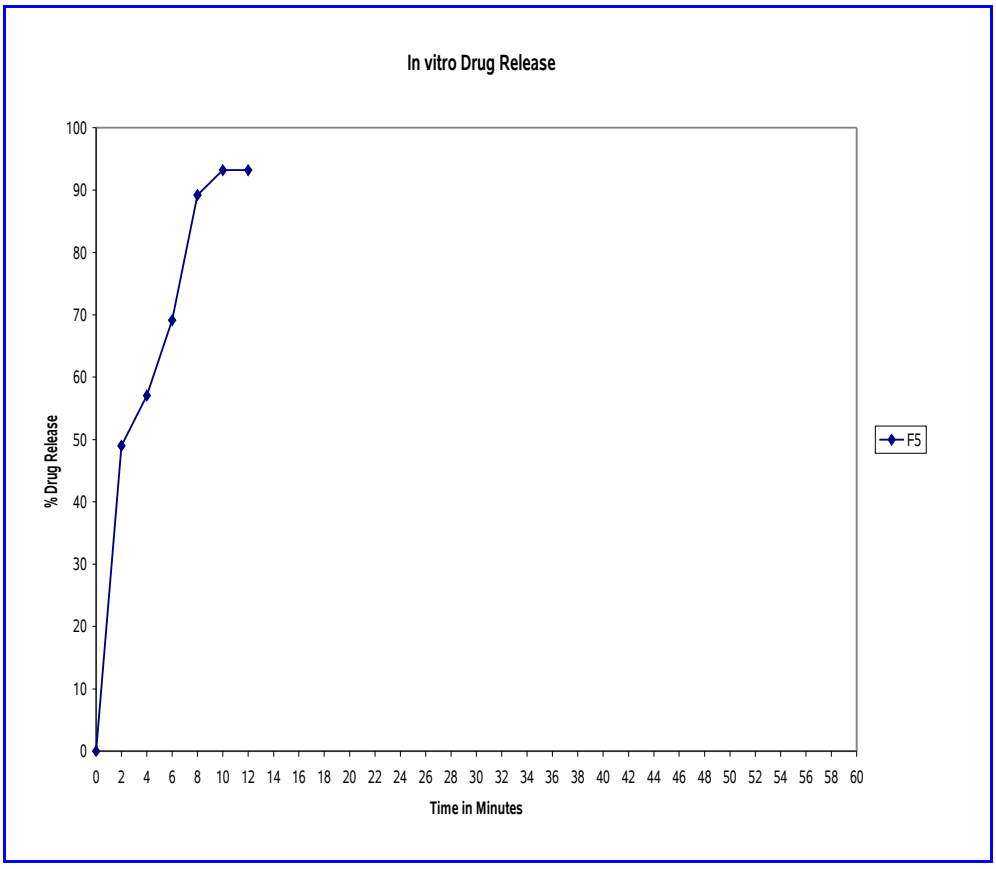


Figure No.13 Comparative *In vitro* Drug Release for F1, F4 and F5

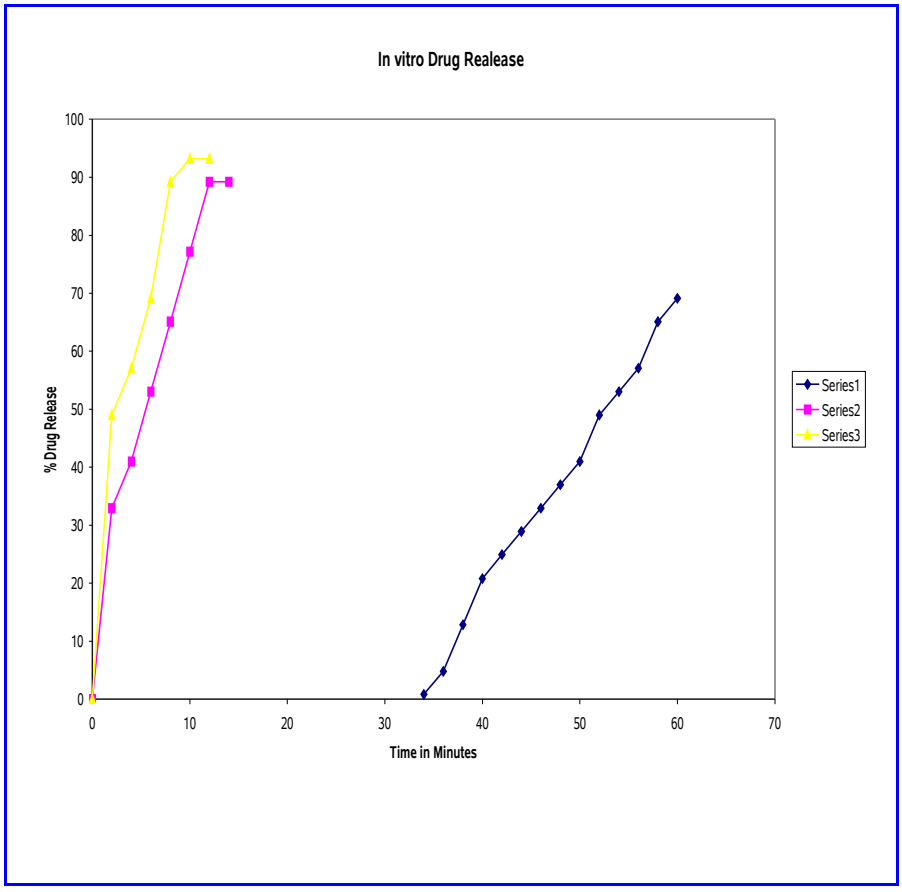


Table No.28 *In vitro* Drug Release

Dissolution profile for mouth dissolving tablets containing salbutamol sulphate prepared by using Cros-Carmellose Sodium in Sorenson's buffer (pH 6.2)

Time in minutes	% Drug Release F1 (Control)	% Drug Release F6	% Drug Release F7
2	-	53.03	57.05
4	-	57.05	69.10
6	-	65.08	85.17
8	-	67.10	89.19
10	-	85.17	97.23
12	-	89.19	-
14	-	93.20	-
16	-	-	-
18	-	-	-
20	-	-	-
22	-	-	-
24	-	-	-
26	-	-	-
28	-	-	-
30	-	-	-
32	-	-	-
34	0.80	-	-
36	4.80	-	-
38	12.85	-	-
40	20.79	-	-
42	24.91	-	-
44	28.92	-	-
46	32.94	-	-
48	36.96	-	-
50	40.98	-	-
52	49.00	-	-
54	53.03	-	-
56	57.07	-	-
58	65.08	-	-
60	69.10	-	-

Discussion

- Dissolution behaviours of controlled tablet has shown in table no.27 and figure no.1 and it was observed that controlled tablets has shown 69 percent drug released at 60 th minute and drug was not completely released due to absences of superdisintegrants in the formulation.

- Dissolution profile of mouth dissolving tablets containing salbutamol sulphate by using cros-carmellose sodium has shown in table no.27 and figure no.6 and 7 it was obsever that the tablet containing 8 percent (F4) and 10 percent (F5) cros-carmellose sodium had shown the drug release 93.20 percentage and 97.23 percentage respectively at 14 th and 10 th minutes, it was found that 97.23 percentage drug release which was quicker than both control and formulation prepared by other superdisintegrants.

- Cros-carmellose sodium is pivotal step in rapid disintegration and ultimately quick release of drug from the tablets.

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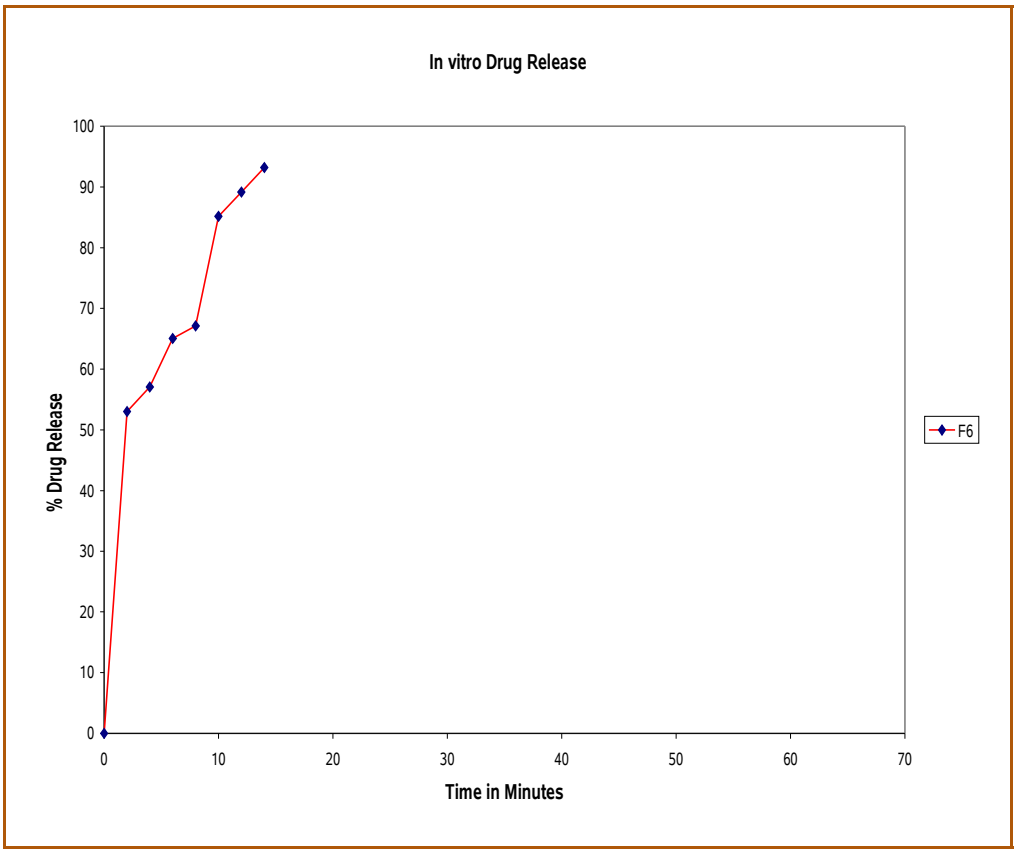
Figure No.14 *In vitro* Drug Release for F6 Formulation



F5

Figure No.15 *In vitro* Drug Release for F7 Formulation

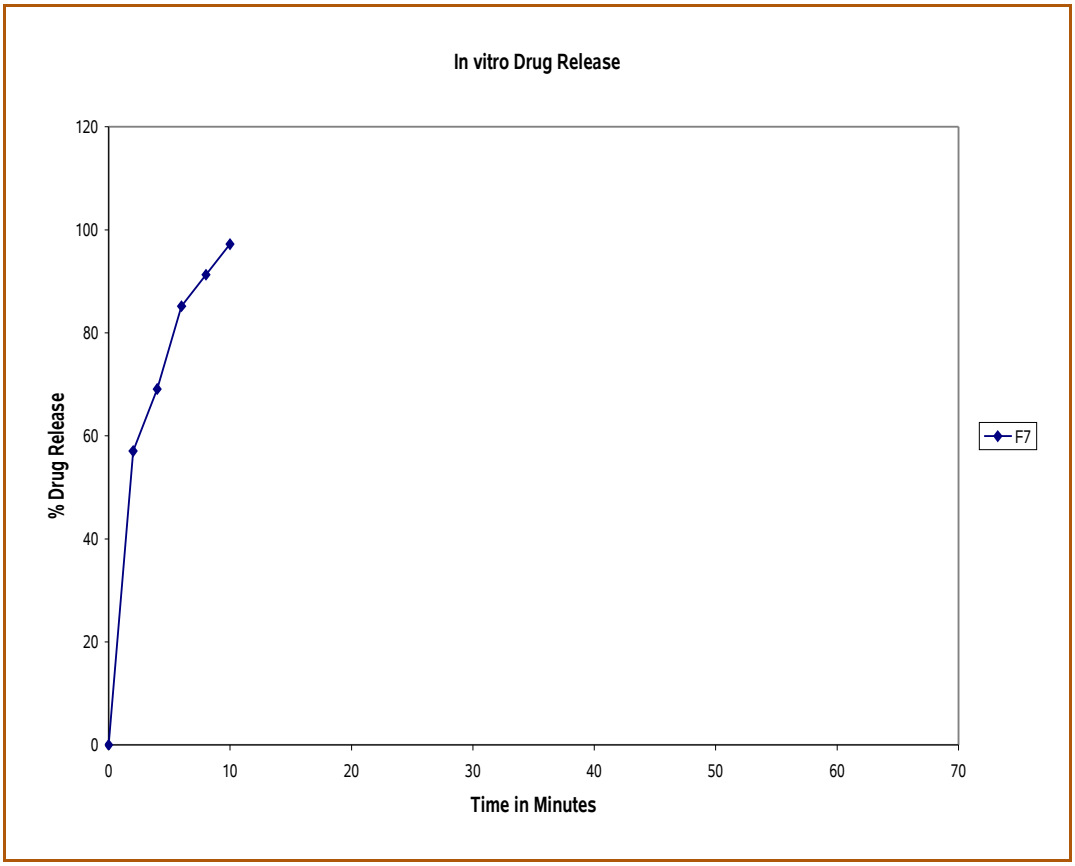
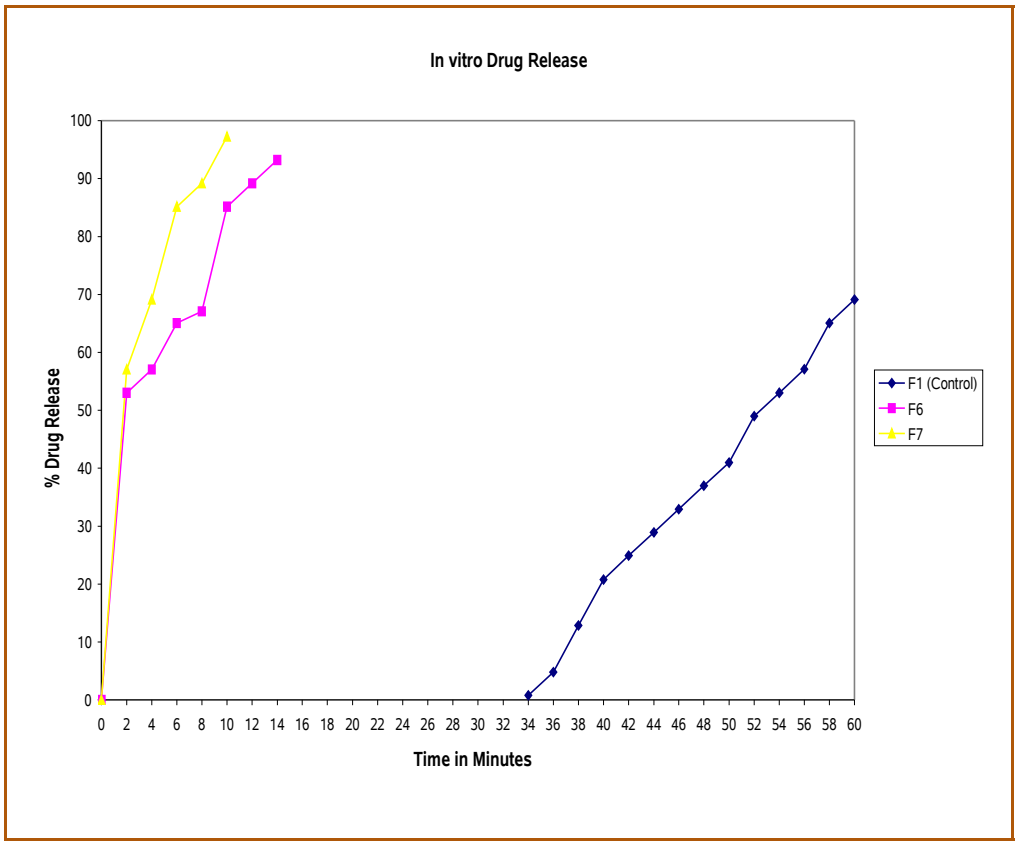


Figure No.16 *In vitro* Drug Release for F6,F7,F5 Formulation



Accelerated Stability studies

TableNo.29 Stability Studies Reports

Time period in weeks	Parameters				
	Weight in mg	**Hardness kg/cm^2**	**Disintegration time in sec**	**Wetting time in sec**	**Drug Content %**
0 day	150	3.5	42	16.3	99.30
1st week	150	3.5	42	16.3	99.25
2nd week	150	3.5	42	16.3	99.25
3rd week	151	3.5	42	16.3	99.20
4th week	151	3.5	42	16.3	99.00

Discussion

The stability studies of the mouth dissolving tablets were studied as per ICH guidelines for the period of one month and the percentage drug content of the formulation complied within the limit as per ICH guidelines.

9. Summary and Conclusion

Asthma is defined as chronic inflammatory disorder of the airways in which many cells a mast cells, esinofils, T-lymphocytes, macrophage, neutrophils and epithelial cells and other cellular elements play role in susceptible individual recurrent episodes of wheezing breathless chest fight and coughing

- Anti asthmatics are typically corticosteroids, leuckotriene cormones, antihistamines, beta two agonist theopylline.
- Salbutamol sulphate is B_2 adrenergic agonist that stimulator receptors of smooth muscles in the lungs. Salbutamol is believed to work by adenylate cyclase, the enzyme responsible for generating cyclic Amp an intracellular mediator. Increased cylase Amp lead to activating of intra cellular ionized cyclic Amp prokinase A which inhibits phosphorylation of myosin and lowers the intracellular ionic calcium concentration, resulting in relaxation of bronchial and tracheal smooth muscles, which in turn relieves branchospasm, reducer airway resistance, facilitates mucous drainage and increases vital capacity
- Geriatric, pediatric and psychiatric patients were less conventional by means of taking their medication it is difficult for many patients to swallow tablets and capsules. Hence they do not comply with prescription which results in high incidence of non compliance and ineffective therapy. Such problems can be resolved by means of mouth dissolving tablets.
- Several methods have been reported for the formulation of mouth dissolving dosage forms, which required water soluble drugs. among

different approaches for preparing mouth dissolving tablets, By using super disintegrant is one of them

- Rapidly disintegration tablet is formulated by wet granulation method using superdisintegrant such as sodium starch glycolate, crospovidone, cros-carmellose sodium and the disintegration time of the mouth dissolving tablets were compared with control formulation (with out super disinter grants).
- Powder blend of all formulation had shown good flowability
- Mouth dissolving tablets of salbutamol sulphate were made with different concentration of superdisintegrants and used for tablet properties and dissolution profile.
- The obtained tablet were subjected to official and unofficial evaluation test via uniformity of weight, hardness, friability test, content uniformity, disintegration time and dissolution test respectively.
- The evaluation study of the tablets reported to be complied with official and the permissible limits him reference to official monograph.
- The dissolution study was carried out to determine the profile of drug release from the formulation
- The dissolution profile for control tablet was observed that 70% drug relecese within one hour.
- Dissolution profile for tablet prepared by F_2 and F_3 as formulation containing 8% and 10% of sodium starch glycolate as superdisintegrants respectively. It was observed that 90% drug release

was occurred in 20 and 12 minutes for F_2 and F_3 formulation respectively.

- Dissolution profile for tablet prepared by F_4 and F_5 as formulation containing 8% and 10% of crospovidone as a superdisintegrant respectively. It was found that 90% drug release was occurred within 12-14 minutes for both formulations.
- Dissolution profile for tablet prepared by F_6 and F_7 as formulation containing 8% and 10% of cros-cormellose sodium as a superdisintegrant respectively. It was found that 95% drug release was occurred within 14 minutes for F_6 formulation, 97% drug release was occurred within 10 minutes for F_7 formulation

- The stability studies of the selected formulation were studied at 40°C and 75 RH for one month. The drug content and physical parameters like hardness and disintegration time were evaluated.

In conclusion,

Now a days inhaler are used for treating congestion due to asthma, it is costly and most of the patient are not satisfy that type of administration.

Mouth dissolving tablets overcome these disadvantages viz it is more economic and release the drug immediately thus improve the patient compliance.

Dissolution rate increases in following manner with increasing the concentration of the superdisintegrants.Control < sodium starch glyolate < crospovidone< cros carmellose sodium as a superdisintegrants showed faster release than control formulation and formulation prepared by other super disinter grants which was pivotal step in rapid disintegration and ultimately to quick release of drug from tablet.

Future Plan:

- Further, to determine the bioavailability of the mouth dissolving tablets by using suitable animal model and confirm their absorption of drug.

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